Lessons Learned from Adapting a Generic Narrative Diabetic-Foot Guideline to an Institutional Decision-Support System

MOR PELEG1, DONGWEN WANG2, ADRIANA FODOR3, 4, SAGI KEREN5 and EDDY KARNIELI3, 4

1 Department of Management Information Systems, University of Haifa, Israel
2 Biomedical Informatics Program, University of Rochester, NY
3 Institute of Endocrinology, Diabetes & Metabolism, Rambam Medical Center and 4 Galil Center, Technion–Israel Institute of Technology, Israel
5 Department of Computer Science, University of Haifa, Israel

Abstract. Clinical guidelines usually need to be adapted to fit local practice before they can be actually used by clinicians. Reasons for adaptation include variations of institution setting such as type of practice and location, availability of resources, differences in patient populations, local policies, and practice patterns. When a guideline is implemented for clinical decision support and integrated with an institution's clinical information system, the data model of the local electronic medical record (EMR) and the data actually collected and stored in it also influence the guideline's adaptation. The purpose of this work is: (1) to characterize a tool-supported process for guideline encoding that addresses local adaptation and EMR integration, and (2) to identify the types of changes in guideline encoding during the local adaptation process.

Keywords: Clinical guidelines, computer-interpretable guidelines, local adaptation, EMR integration, GLIF3

Introduction

Clinical guidelines are systematically-developed statements to assist practitioner and patient decision making about appropriate healthcare for specific clinical circumstances [1]. They aim to improve quality of care, reduce unjustified practice variations, and control costs. Studies have shown that computerizing guidelines as decision-support systems (DSSs) is more likely to generate positive impacts when compared to paper-based guidelines [2]. Therefore, many researchers have been developing languages to represent guidelines in computer-interpretable formats [3].
Clinical guidelines developed by government agencies or medical specialty organizations at the national level usually need to be adapted to fit the local practice before they can be actually used by clinicians at specific institutions. Reasons for such local adaptations include variations of institution setting, such as type of practice (e.g., hospital vs. physician office) and location (e.g., urban vs. rural), availability of resources, difference between patient populations (e.g., as reflected in prevalence of a disease), local policies, and practice patterns [4, 5]. Successful guideline implementation has to be supported by organizational efforts [6]. At the same time, there are many technical issues that should be addressed, especially when implementing guidelines as clinical decision support systems (CDSSs).

Several groups have reported their experiences when adapting narrative clinical guidelines and implementing them as CDSSs. Shiffman investigated the validity of guideline knowledge and suggested methods to assess the logic integrity of the original guideline, such as completeness and consistency of decision recommendations. An exhaustive set of possible values for each variable should be determined and special attentions should be devoted to the logic combination of variables within decision criteria [7]. HieroGLIF [8] and CAMINO [9] are approaches that separate the site-independent information of guidelines from site-specific information. Based on the theory of axiomatic design (AD), HieroGLIF is an extension of the GLIF3 [10] guideline modeling language, supporting hierarchical modular guidelines, starting from broad objectives and ending with details of the recommendations. Guidelines are specified in a setting-independent manner and are then locally adapted by each practice. Changes occur mostly at the lower, more detailed levels of the design tree. CAMINO is a tool that allows formalizing site-specific customizations, including: (1) annotations documenting the guideline authors' assumptions, (2) a model of organization activities, resources, policies, and preferences, and (3) rules that define allowed transformations that make a generic guideline site-specific. GLARE [11] takes a different approach to adaptation of a guideline. The resources needed by each action of the guideline are explicitly declared. Then, a context-specific guideline is built from the general one by collecting only those paths that require available resources. Tierney et al. investigated the practical considerations when adapting an inpatient heart failure guideline to the outpatient setting and implementing it within an electronic medical record (EMR) [12]. About one-third of the original guideline’s recommendations were not included in the new implementation because of the differences in the setting. In addition, they had to translate some of the guideline’s data definition into multiple EMR entries as the original definitions of these data in the guideline were not directly available from the local EMR.

These works referred to two types of processes: (1) adaptation needed in order to formalize a textual guideline, including knowledge interpretation and validation of the completeness and correctness of guideline knowledge, and (2) adaptations needed to fit the context (including local procedures, resources, and EMR). In this paper, we address mainly the second kind of adaptation, to which we refer as local adaptation. Our study has two specific purposes: (1) to identify and classify specific types of changes in guideline encoding during the process of local adaptation of a guideline for clinical decision support, and (2) to suggest a process for local adaptation that addresses the issue of data availability, clinical workflow, and validation of encoding. These are important issues that need to be addressed whenever a guideline encoding is shared, i.e., implemented and integrated with EMR systems at a local institution.
1. Methods

To adapt a generic guideline in narrative format as a CDSS at a local institution, we assumed: (1) clinicians’ needs of decision/management support services from a computer system have already been identified, and (2) a paper guideline has already been chosen as the source of medical knowledge such that it can be adapted for implementation. We used the GLIF3 [10] guideline modeling language to encode guidelines. A GLIF3 encoding of a guideline includes a visual clinical algorithm that specifies a process of care, depicting patient states, medical tasks, and clinical decisions, all embedded within a specific workflow. The medical tasks, such as prescriptions of drugs and orders of lab tests are specified by concepts taken from controlled vocabularies. The decision criteria are specified through logic expressions that reference clinical concepts, which are then mapped to EMR data. We chose Protégé-2000 [13] as our vehicle for guideline encoding in GLIF3.

We analyzed the encoding of a diabetes foot care guideline developed by the American College of Foot and Ankle Surgeons [14], which was selected by our clinician experts for implementation. Our analyses focused on changes that were made throughout the process of translation of the original guideline into the GLIF3 format as well as its integration with a local EMR. The front-end of the EMR is a web-based patient clinical record, developed by one of the authors (EK), which is used by clinicians to manage diabetic patients, from local as well as remote clinics. The system uses an internet browser as a user-friendly interface and an Oracle database server located at the Rambam Medical Center is the backbone of the system. A built-in internal email application serves for communication between the clinicians and consultants while reviewing of the data. Our final goal was to integrate guideline recommendations with this system.

The process to encode and to adapt the narrative guideline consisted of:

Step 1 – translation of the original guideline into GLIF3 format. One of the informaticians on the team (MP) first performed a high-level encoding in GLIF, where decision criteria were written in English, rather than using formal notation. The encoding was based only on the original narrative guideline without consideration of local adaptation. The rationale of doing this was to facilitate communication with clinicians, since the initial conceptual flowchart created at this step could show patient management process, and thus the clinicians would understand better how the guideline could fit with their usual workflow. At this stage, we only specified the initial version of the conceptual algorithm with a high-level description of the action steps and the decision steps written in English rather than in GLIF3’s formal definition.

Step 2 – analyses of local practice. After the initial encoding was completed, the two expert clinicians in our team (EK, AF), together with an informatician (MP), clarified the definitions of concepts, matched the data items of the initial encoding to the data entities in the local EMR, and analyzed the fitness of the guideline to the local setting and workflow.

Step 3 – revision of the initial encoding. Based on the analyses in the previous step, we made revisions to the initial encoding such that: (1) it fit with local practice, and (2) it included formal definitions of data queries and decision criteria that were mapped to the EMR’s schema and available data.

Step 4 – validation: manual check of encoding. The clinicians and informatician manually checked the clinical algorithm, formal definitions of decision criteria, and mapping of concepts to the EMR schema.
Step 5 – validation: execution of test cases by informaticians. For further validation, MP and DW used the GLIF Execution Engine (GLEE) [15] to apply the encoded guideline to test cases. For this purpose, SK integrated GLEE with the back-end Oracle database of the local EMR, so that GLEE can directly query the patient data of the test cases. We invoked the guideline in an interactive mode, following the path of execution when it was applied to a specific case. For the purpose of validation, we used 14 real cases and 6 simulated cases. The simulated cases supplemented the real cases by testing branches of the clinical algorithm that were not tested by the real cases. The Human Rights Committee of Rambam Medical Center approved the study, and written informed consents were obtained prior to adding patient data to the EMR. Figure 1 shows a screenshot of the guideline being executed by GLEE.

It is important to note that the validation (steps 4 and 5) was an iterative process. When problems were found in steps 4 and 5, we went back and repeated steps 2 and 3.

---

**Figure 1.** A screenshot of the diabetic foot guideline being executed by GLEE. Squares indicate Action Steps, hexagons – decision steps, circle with ‘p’ on it – Branch Step, and blank circles – Synchronization Steps. GLEE enables parallel execution. The branch step at the top of the figure enables parallel execution of three parallel paths dealing with different foot problems: ulcer (left path), infection (middle path), and Charcot (malalignments of the foot bones – right path). The two action steps “ulcer refer to none” and “Infection referral to none” set flag variables that guard that referrals, due to ulcer or due to infection, are made only once during the algorithm. At anytime, one of the currently active steps can be chosen to execute. In the figure, the three steps with bold contour are active, each belonging to a different path of the three paths explained above. The one with the heavy black contour, labeled “Assessment of non-infected Foot ulcers”, is chosen to be executed, leading to entering a subguideline. GLEE evaluates decision criteria, based on patient data stored in the EMR, and automatically suggests which branch to follow. In the figure, the ‘Ulceration?’ Decision was evaluated and the ‘Ulcer’ path has been followed.
Step 6 – validation: execution of test cases by expert physicians. A year after the guideline was finalized, we decided to develop a new user-interface for the system. In preparation, we carried out another round of validation and updates that considered different types of patient-clinician encounters: those that constitute the main care algorithm and those that are follow-up sessions (follow-up on antibiotic treatment).

2. Results

During the iterative encoding process, we found that we had to clarify a few concepts that were important for decisions. In addition, we had to change the guideline encoding in different ways to fit with the local setting, practice, and workflow. Here, fitting with local setting concerns the availability of resources that depends on the type of institution and its location, fitting with local practice concerns the different treatment selections that depend on local policy or patient population, and fitting with workflow concerns the delivery of guideline recommendations that could be seamlessly integrated with clinicians’ practice. When integrating the encoded guideline with the local EMR, we found that we had to further revise the guideline’s encoding to map to the unique data model at the local site and to address the issue of data unavailability (never collected by clinicians even though they were modeled in the EMR schema). These revisions were significant, affecting the conceptual flowchart, the definition of data items, and the formal specification of decision criteria.

2.1. Clarifications of concepts

The original guideline contained implicit background knowledge. For example, the definitions of a few high-level concepts (e.g., ischemic symptoms) were not explicitly given. In addition, several data items in the original guideline were not fully specified (e.g., the data type and expected value of ulcer margins). Specifically, the original guideline contained ten concepts that were used at decision points of the guideline (e.g., neuropathy or not). Two of them (neuropathy, inflammation) were not defined explicitly and our expert clinicians had to provide clarifications for them so that they could be mapped to EMR data items. One concept definition had to be changed to fit with the local practice (PVD), see Figure 2(a). The definitions of six other concepts (charcot, pulses present, normal results for non-invasive tests, inflammation, limb-threatening infection, infection) were restated according to the EMR schema and available data (Figure 2(b)), while conserving the meaning of the original guideline. In the validation phase, the definition of neuropathy was changed again because the clinicians were not satisfied with their previous definition.

2.2. Fitting with local setting

The setting of outpatient clinics in which the guideline is being implemented in Israel is different from that assumed by the American guideline. For example, in the Israeli setting, family practitioners refer patients to orthopedic or plastic surgeons for wound debridment (i.e., surgical removal of dead tissue from a wound); while in the US, this is performed at the local clinics. Thus at step 2, we made three changes to guideline encoding to fit with our setting: (1) patients who have charcot malalignments should be referred to a hospital or diabetic foot clinic, instead of being managed by primary
practitioners as suggested by the original guideline, (2) patients with severe ulcers should be referred to hospitals for treatment, instead of having their wounds debrided by the primary practitioner, and (3) primary practitioners cannot give parenteral antibiotics to patients with non limb-threatening infection, but only oral antibiotics, which are easily administered by the patients themselves at their own homes. At the validation step, we made another change of this type: transcutaneous oximetry should be ordered only if the patient is referred to be hospitalized.

<table>
<thead>
<tr>
<th>(a) Change to fit with local practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial encoding:</strong></td>
</tr>
<tr>
<td>pulse_popliteal = false or</td>
</tr>
<tr>
<td>pulse_femoral = false or</td>
</tr>
<tr>
<td>pulse_dorsalis_pedis = false or</td>
</tr>
<tr>
<td>pulse_posterior_tibial = false or</td>
</tr>
<tr>
<td>cyanosis = true</td>
</tr>
<tr>
<td><strong>Final encoding:</strong></td>
</tr>
<tr>
<td>// absent popliteal or femoral pulses of either foot</td>
</tr>
<tr>
<td>pulse_popliteal_L_absent = &quot;Yes&quot; or pulse_popliteal_R_absent = &quot;Yes&quot; or</td>
</tr>
<tr>
<td>pulse_femoral_L_absent = &quot;Yes&quot; or pulse_femoral_R_absent = &quot;Yes&quot; or</td>
</tr>
<tr>
<td>// blue skin in addition to a diminished pulse or missing posterior-tibial or</td>
</tr>
<tr>
<td>// dorsalis pedis pulse</td>
</tr>
<tr>
<td>(skin_color_blue_purple = &quot;Yes&quot; and</td>
</tr>
<tr>
<td>(pulse_popliteal_L_diminished = &quot;Yes&quot; or pulse_popliteal_R_diminished = &quot;Yes&quot; or</td>
</tr>
<tr>
<td>pulse_dorsalis_pedis_L_absent = &quot;Yes&quot; or pulse_dorsalis_pedis_R_absent = &quot;Yes&quot; or</td>
</tr>
<tr>
<td>pulse_dorsalis_pedis_L_diminished = &quot;Yes&quot; or pulse_dorsalis_pedis_R_diminished = &quot;Yes&quot; or</td>
</tr>
<tr>
<td>pulse_posterior_tibial_L_absent = &quot;Yes&quot; or pulse_posterior_tibial_R_absent = &quot;Yes&quot; or</td>
</tr>
<tr>
<td>pulse_posterior_tibial_L_diminished = &quot;Yes&quot; or pulse_posterior_tibial_R_diminished = &quot;Yes&quot;)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) Change to map to EMR schema</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial encoding:</strong></td>
</tr>
<tr>
<td>charcot = true</td>
</tr>
<tr>
<td><strong>Final encoding:</strong></td>
</tr>
<tr>
<td>(mal_forefoot_L = &quot;Yes&quot; or mal_forefoot_R = &quot;Yes&quot; or</td>
</tr>
<tr>
<td>mal_mid_L = &quot;Yes&quot; or mal_mid_R = &quot;Yes&quot; or mal_hind_L = &quot;Yes&quot; or mal_hind_R = &quot;Yes&quot;)</td>
</tr>
<tr>
<td>and redness = &quot;Yes&quot; and swelling = &quot;Yes&quot;</td>
</tr>
</tbody>
</table>

Figure 2. The initial and final encoding of decision criteria. (a) decision criterion for peripheral vascular disease (PVD) was changed to fit with the local practice. According to the original guideline (initial encoding), four pulses were measured in each leg, and if at least one of them was absent, or if the foot color was blue (cyanosis), then PVD was concluded. The local practice (final encoding) is that the physician documents whether a pulse is missing or diminished. If either the popliteal or the femoral pulse is absent in either the right (R) or left (L) foot, it is sufficient to conclude PVD; but if these pulses are diminished, or if either the dorsalis pedis or the posterior tibial pulse is absent or diminished, the foot color should be blue in order to conclude PVD. (b) The initial decision criterion for charcot was changed to map to the EMR schema. In this case, the information on whether a patient has charcot is dispersed over many EMR fields that designate areas of malformations of the foot: forefoot, mid-foot, hind-foot. To conclude Charcot, signs of redness and swelling have to be present in addition to malformations.

2.3. Integration with workflow

We made one change to the guideline encoding in step 2 to integrate with clinical workflow. Our clinicians noted that although the guideline defined criteria to categorize ulcer grade, this function was not required in the implementation because determination of ulcer grade was performed at EMR data entry after physical exam. At
the validation step (step 4), we made three additional changes: (1) two courses of antibiotics (instead of one in the original guideline) should be tried to treat infection before referring the patient to a hospital, (2) telemedicine consultation was added to determine ulcer staging, and (3) the clinical algorithm of the encoded guideline was rearranged so that all of the referral actions were put into one place of the top-level guideline to fit with the referral task in practice. At validation step 6, we introduced two changes relating to workflow integration: (1) the design of the encoded guideline was changed to reflect different encounter types, and (2) adding decision-support for determining ulcer grade that could be used if the grade was not determined during data entry. Note that this change overrode the second category of changes made at step 4, as described earlier.

2.4. Matching with local practice

We made three changes to match with the local practice: (1) the decision criteria for suspecting PVD were changed (Figure 2a), (2) several medical actions were added (e.g., ordering EMG) or removed (e.g., clonus testing), and (3) a physician who encounters a patient with non-life-threatening infection may treat him with antibiotics as suggested by the guideline, or may decide to refer the patient to a hospital or clinic.

2.5. Consideration of data retrieval

To ensure that the guideline can be directly applied to specific patient cases, we studied the EMR schema and the available data. We identified 188 data items of the encoded guideline that should be mapped to the data fields of the local EMR. The EMR schema and the availability of data actually collected and stored in the EMR affected the encoding of decision criteria in the following ways.

- Multiple guideline concepts could be mapped to a single EMR data item. For example, both abscess and fluctuance were mapped to abscess.
- A single guideline concept could be mapped to combinations of multiple EMR data items. For example, charcot was mapped to redness, swelling, as well as one of the six different data items that describe malformations in different locations of the right or left feet (see Figure 2(b)).
- Guideline concepts missing in the EMR schema. The expert clinicians decided whether to remove the unavailable data items from the definitions of decision criteria or to change the EMR schema such that the relevant data can be collected.
- Data unavailability despite the fact that the EMR schema allowed easy mapping. For example, while there was an EMR field to record the existence of ulcers, the data were never actually collected in our EMR.
- Mismatch of data type and definition of normal ranges. For example, the guideline refers to a test result that needs to be greater than 1.3, whereas the EMR stores the values as three possible strings: greater_than_1.1, less_than_0.5, between 0.5_0.9.

2.6. Changes of guideline encoding

The local adaptation process had significant affects on the encoding, including change of algorithm design, definition of decision criteria, and specification of data items that
are referenced by the decision criteria. Table 1 shows the number of knowledge components created during the iterative encoding process. The number of components that define the structure of the algorithm – action and decision steps – decreased significantly during the local adaptation step, resulting in version 1. This was mainly due to the removal of the charcot branch of the algorithm to fit with our setting. Although the direction of the change (reduction) is only specific to this guideline, we believe that in general, the most significant scale of changes in the structure of the clinical algorithm will occur during this stage. The number of decision steps increased during the validation step, mostly due to the change of the algorithm's design to group all decisions regarding referrals to a single place in the top-level guideline.

Table 1. The number of guideline components and changes made at different steps of encoding.

<table>
<thead>
<tr>
<th>Knowledge Item</th>
<th>Versions</th>
<th>Original</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision steps</td>
<td></td>
<td>23</td>
<td>13</td>
<td>13</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Action steps</td>
<td></td>
<td>84</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>73</td>
</tr>
<tr>
<td>Decision criteria</td>
<td></td>
<td>9</td>
<td>52</td>
<td>52</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>Data items</td>
<td></td>
<td>15</td>
<td>73</td>
<td>66</td>
<td>150</td>
<td>157</td>
</tr>
</tbody>
</table>

Original – original encoded version; V1 – version 1 created after locally adapting the guideline with the clinicians (steps 2 and 3); V2 - version 2 created after the initial clinical validation (step 4 and 5); V3 – semi-final version created after iterative validations; V4 – final version created at validation step 6

The components that define the computable specification include decision criteria and data items. During the creation of the original encoding, the informatician wrote the majority of the decision criteria in English. According to our local adaptation process, formal definitions are created during the local adaptation phase, and are changed during the validation phase, as reflected in Table 1. The number of data items increased during the validation phase, in which the mapping of guideline concepts to EMR terms was determined, often involving mapping a single guideline concept to multiple EMR terms.

We validated the guideline using GLEE by executing 14 real patient cases from the EMR, supplemented by six simulated cases to cover all paths through the algorithm. The validation considered 22 branching points and recommendations. At the end of the validation, all 22 criteria matched with the expected results.

During a later phase of the development of our guideline-based DSS, which addressed a different user interface for the system, the guideline was revised (as described in section 2.3). We carried out a validation study (paper in preparation) in which eight clinicians evaluated the correctness of the encoding based on the recommendations given by the CIG to a simple and a complex patient scenario. This evaluation resulted in a change to one of the action steps.

3. Discussion

As manifested by the works covered in this book, the community of researchers in the field of computerized guidelines has been recently focusing on the following issues

- Achieving high-quality and safe guidelines by using ontologies to formally represent guidelines (Dominguez et al., [10]) and formal methods to verify
guideline encodings (Terenziani et al., Chesani et al., Hommersom et al., Balser et al.)

- Shortening the life-cycle of implementation of guidelines as DSSs, by:
  - Gradually marking up narrative guidelines and transforming them into computer-interpretable representations (Hatsek et al.)
  - Supporting local adaptation of guidelines and their integration with local systems (Hommersom et al., Patkar et al., [4])
  - Allowing for sharing of CIGs by multiple implementing institutions [10]
  - Developing tools to support the guideline life cycle, such as guideline editing, verification (see above), and execution (Votruba et al.)

Our work fits within these current research trends; our thorough encoding and verification process was carried out in order to achieve a high quality CIG, encoded in the GLIF3 ontology, suitable for the local environment, and integrated with the EMR.

We proposed a process for translating a narrative guideline and adapting it as a CDSS in a local institution. This process used tools to support encoding and validation. We focused on changes made during a local adaptation process. This is in contrast to other studies that focused on the changes during the development of the original clinical algorithm without considering a computable representation [16] or the maintenance of a guideline to reflect the latest development in medical knowledge [17].

The process that we carried out involved initial encoding of the original guideline by informaticians. This approach has benefits and drawbacks. Starting the encoding from the original guideline makes it potentially possible to adapt it for use by several local institutions with modifications to specific parts of the general encoding. Indeed, the lesson we learned is that a significant portion of the original guideline is useful for the local site. This approach also makes it easier to communicate with clinicians to demonstrate the system to them, to identify the potential problems of the original guideline, and to find appropriate solutions to a local implementation. However, if we only care about implementation at a specific site, changing the process by having informaticians and clinicians working together as early as possible would save time, especially when significant parts of the original guideline need to be changed. A final lesson we have learned about the development process is that we should consider integration with EMR as early as possible, as it also has major impacts to the encoding.

One of the goals when developing the GLIF3 model was to allow sharing of encoded guidelines among institutions and platforms. Changes of guideline encoding due to differences in local setting, practice, and workflow seem to be inevitable. Further investigations are required to study whether it is possible and, if it is, how to separate the medical knowledge from the organizational knowledge when developing guidelines from clinical decision support. Obviously, the encoding of data items should not include proprietary terms or codes belonging to some institution's EMR, but rather should refer to a virtual medical record that defines a high-level structure of clinical data based on controlled vocabularies (e.g., SNOMED-CT [18]). Because right now there is little consensus on such a virtual medical record, our implementation was based on a 1:1 mapping between concept identifiers and fields of EMR tables, which is a limitation. Work in progress includes a mapping ontology that would allow encoding the guideline in GLIF through clinical abstractions and mapping to the actual EMR tables. This mapping ontology would support the definition of temporal (e.g., current,
recent) and taxonomical (e.g., antibiotics) abstractions that would simplify guideline encoding in GLIF without the need to change the GLIF language.

Our work enabled us to test the potential ways in which guideline-based interventions could be integrated with the clinician’s workflow. Our ongoing work involves the integration of the decision support functions within the web-based user interface that the clinicians currently use to enter data into the EMR. Our long-term goal is to evaluate the impact of the system to clinical process and outcome, such as documentation of patient data, order of lab tests, and patient performance.

Acknowledgements

We thank Mr. A. Kulater for his excellent technical assistance. EK was supported by grants from Israel National Institute for Health Policy and Health Services Research and Galil Center for Telemedicine and Medical Informatics. We thank the anonymous reviewers for their suggestions.

References