Author's response to reviews

Title: Closed-loop insulin delivery for treatment of type 1 diabetes

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Author's response to reviews: see over
Dear Editor,

Thank you for arranging a careful review of our paper and annotating the manuscript with detailed suggestions. We are grateful for the majority of constructive comments by the Reviewers, which we took onboard together with the editorial comments when preparing the revision.

We reviewed the manuscript accordingly and submit the revised manuscript with annotations and also include response to all the points raised.

Thank you for your attention to our work.

With best wishes

Roman Hovorka
EDITOR’S COMMENTS:

1. Abstract: The abstract is a vital part of the article, to encourage browsing readers to download the full text, so must be engaging and informative. The current abstract is well written, and I have only requested that you include an additional sentence of more general introduction.

RESPONSE: A sentence of more general introduction on diabetes has been included in the abstract.

2. Introduction: BMC Medicine has a general medical audience, so researchers and clinicians from many different specialisations may read your article. Therefore the “basics” of your review topic should be clearly introduced at the start of the article, which I think you have done a good job of, and I have no further comments on this section.

RESPONSE: Thank you

3. Main text: Both referees have asked for additional clarification or expansion, which has been annotated for your attention. Referee 1 specifically suggested that you might include a table outlining the achievements in near normal glucose control in recent studies. Referee 2 has suggested that you somewhat change the structure of the main sections, as well as revising your discussion in the final sections to be more relevant to the issue and reduce repetition of already accepted issues focus more on some of the emerging issues. Finally, I have suggested that you provide clarification of the different concept using a text box.

RESPONSE: As suggested, we included a table (Table 2) outlining achievements on closed-loop glucose control in recent studies. A textbox (Table 1) has also been included to list and describe the various closed-loop approaches.

4. Main text: In some sections, you provide a lot of detail, and in others, you provide less detail, where I felt that it would be beneficial for the readers to have more information. I have annotated several spots where I thought you should be more specific with your detail, especially as some of these are points that you promise a discussion of in the introduction. So, for example, in the The future: Perfecting
closed loop, I have suggested that you include detail about how you feel telemonitoring will contribute to enhancing safety of closed loop delivery.

RESPONSE: Thank you for the annotations. These have been responded to (see annotations in the revised text).

5. Figures: Thank you for including visual display elements in the piece. It is your responsibility to gain permission from the copyright holder (usually the publisher) to reproduce any figures and tables that have been previously published. Please confirm that Figure 1 was drawn for this manuscript, if not, please cite a source, and obtain copyright permission if required. Figure 2 are two graphs that you say are adapted from a source that is currently in press. Could you please provide the original figures for our review and/or explain how you have adapted the figure.

RESPONSE: Figure 1 was adapted from author’s own manuscript (panel A) and permission is not needed (Nature Endocrinol Rev rules). Panel B of Figure 1 is drawn for this manuscript. Figure 2 was taken (without any modification) from author’s own manuscript and permission obtained.

6. Conclusions: These are mainly well written, however, I felt that they could be more specific in places, and I have annotated these for your attention.

RESPONSE: The conclusions were modified as suggested.

7. References: Please add the references recommended by the reviewers, and check the main text carefully to ensure central statements are supported by appropriate citations, and that you have covered all the literature that should be covered. Older data can be referenced with an appropriate review, but newer results should be acknowledged with the primary citation. Please also check the references carefully to ensure they are complete? no missing dates, journal titles or page ranges etc.

RESPONSE: The reference section was reviewed carefully and recommended references were included.
This review is a well-presented summary of the recent developments of closed-loop insulin delivery. The contributions of the authors in these recent advances give a high value to their manuscript. The perspectives are also of interest.

RESPONSE: Thank you.

Minor but necessary revisions should include:

1- A mention of recent innovative approaches in terms of MPC algorithms based on multimodular structure, control to range and ‘zone’ MPC control:

RESPONSE: These studies were included in the manuscript, as suggested.

2- A table that summarizes the achievements in terms of near-normal glucose control of the various recent clinical trials using different types of algorithms would be useful to illustrate the current safety and effectiveness of closed-loop insulin delivery to the readership. It would also support the open perspectives for home use.

RESPONSE: Table 2 with a summary of achieved results was included in the manuscript.
Major Compulsory Revisions

1. The authors report that they review the current status of closed-loop insulin delivery systems extending previous work [9,10,11,12], with reference 9 being a review article published by their group on the same topic in February 2011 (Closed-loop insulin delivery: from bench to clinical practice, R. Nat. Rev. Endocrinol. 7, 385–395 (2011)). (references 10-12 refer to a 2006 review by this group, a 2005 review by Steil, and a 2006 review by Renard focused on implantable pumps and sensors). Given the Feb. 2011 review by this group, the authors need to focus on what has changed since then, and avoid repeating arguments and Figures.

RESPONSE: Thank you. We took the comments on board and added new visuals/tables.

2. In addition to not repeating text or having the same Figures, the authors should be consistent in how algorithms are classified. Having "Suspended Insulin Delivery" and "Nighttime closed-loop" categories in both reviews, followed by "Day and Night closed-loop", and "Dual-hormone closed-loop" and "Other approaches" in the earlier review (R. Nat. Rev. Endocrinol. 7, 385–395, 2011) and "Fully closed-loop versus Closed-loop with meal announcement" as a single category in this review creates confusion. The reviewer would recommend following a progression of increasing automation:
   • Suspended insulin delivery 25, 26-29, 31-35, 36, and 37
   • Overnight closed-loop22 38,39, 40,41,42, 43 44
   • Closed-loop with meal announcement 10 24 41 44
   • Fully closed-loop

where numbers indicate references discussed by the authors in each of the section as written. More important is that each section identifies the clinical studies that have been conducted for each of these approaches with all the existing studies being identified and correctly categorized. For this, a clear definition of what constitutes a “Suspend Insulin Delivery Study” from an “Overnight Closed-loop study” versus “Closed-loop with meal announcement” and “Fully closed-loop”. Clearly, a 30 hour closed loop study includes a “nighttime”, and during the night the pump may be “suspended”, making it possible to discuss the study under multiple headings. This should be avoided. What the reviewer would suggest is classifying each study according to the highest level of control achieved – thus a closed-loop study that includes day and nighttime control with no meal announcements would be classified...
as “Fully closed-loop”; a study controlling meals with announcement would be classified “Fully closed-loop with meal announcement”, a study of nighttime control without meals but with the control allowed to increase insulin would be classified as “Nighttime control”, and a study that was limited to a pump suspend was be classified as “Suspend”. Studies should appear one category only with reference to primary (first) manuscript published on that study (manuscripts generated from secondary analysis should be identified). Using this approach, clinical studies could be grouped as:

- Suspended insulin delivery [36, 37, (38)]
- Overnight closed-loop [40, 42, (84)]
- Closed-loop with meal announcement [44, {23, 55}, (25, 60)]
- Fully closed-loop [22, 41, 43, {51}]

where the reviewer has indicated studies referenced in the present manuscript at some point, but not discussed under the existing headings by {}, and reconciled the list with closed-loop clinical studies previously identified by this group in their Feb 2011 review (reference 9 of this report), identifying in (). It is unclear why these studies were reported in the earlier review and not included here. One addition study by Bruttomesso D (J Diabetes Sci Technol. 2009 Sep1;3(5):1014-21) should also be referenced and discussed if it includes closed-loop data. In total, the list only includes 16 studies which even if included in the prior review should still be mentioned in this review.

RESPONSE: We have updated the references as suggested and followed the suggested structure in Table 2. The structure of the main text (albeit with minor modifications) is suggested to be retained allowing to contrast more naturally the “fully closed loop” and “closed loop with meal announcement”.

3. There are far fewer clinical closed-loop studies than a casual reader might infer from reading the present manuscript. This is primarily due to the large number of simulation studies that have been conducted. When reading a tile such as "An improved PID switching control strategy for type 1 diabetes" [14] it may not be clear to many readers whether the manuscript reports clinical data or simulation data (in this case simulation). There are numerous examples of this: "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes", "A model-based algorithm for blood glucose control in type I diabetic patients", "A closed-loop artificial pancreas using model predictive control and a sliding meal size estimator", "Closed-loop control of artificial pancreatic Beta-cell in type 1 diabetes"
mellitus using model predictive iterative learning control” where it is not clear from the title or text if the reference is to a simulation, animal, or clinical study. Although simulation studies are unquestionable useful, they carry substantially less weight than clinical or animal studies.

What is needed in the present manuscript is a clear indication to the reader as to which studies/manuscripts are reporting clinical data and which are reporting simulation data.

RESPONSE: Where appropriate we indicated papers which are “non-clinical”.

4. The authors have provided some discussion of simulation studies (in silico studies). Simulation studies do play an increasingly important role in advancing closed-loop research; however, the authors have referenced on two of the many models used to perform these simulations (a model the authors developed at Cambridge [45] and a model developed at the University of Virginia (UVA) [46]). Of these two it unclear what is different. They report their model to include inter and intra-subject variability but do not comment on whether the UVA model also has these features, leaving the reader to infer that it does not. What is needed is a clear statement about what differentiates their model [45] from the UVA model [46]. It should also be pointed out, with some expanded discussion, that the UVA [46] model has been accepted in the US as a replacement for animal studies (the authors should confirm the exact FDA status) and acknowledge other models that have been used. At a minimum, the model used by Medtronic Diabetes (J Diabetes Sci Technol. 2009 Sep 1;3(5):1047-57, Diabetes Technol Ther. 2005 Feb;7(1):94-108.) should be discussed as that model was used in developing the Medtronic PID controller which accounts for 1/3 of the referenced studies describing closed-loop insulin delivery with meals (references 23, 41, and 43).

RESPONSE: We modified the section as requested.

Minor Essential Revisions
1. "In silico studies play a crucial role to complement clinical testing and address scenarios which cannot be practically or ethically tested in clinical studies [45,46]" - should read “in clinical” with a space between in and clinic.

RESPONSE: Done – thank you.
2. Glucose control around meals has been shown challenging in laboratory studies both in adults and young people [43,41] – should read either “has been” or “was”. The author might also consider using “inpatient” to describe these studies rather than “laboratory” (people are studied in clinics; animals are studied in laboratories).

RESPONSE: Done.

Discretionary Revisions
1. The authors should consider shortening the sections relating to HOME STUDIES AND BEYOND, EXPECTATIONS FOR CLINICAL PRACTICE, THE FUTURE: PERFECTING CLOSED-LOOP as much of the material in presented in these sections seems rather obvious. For example:
   a. When moving towards home studies, the emphasis should be on recognising real-life conditions whilst providing appropriate support from the research team.
   b. Pilot studies may evaluate efficacy, safety and utility over a short period of time, whereas longer studies are needed to demonstrate effectiveness on glycaemic control and rates of hypoglycaemia.
   c. The main goal of closed-loop therapy is to achieve good glycaemic control whilst reducing the risk of hypoglycaemia in people with type 1 diabetes.
   d. Alongside the benefits of closed-loop therapy, it is essential to set realistic goals to keep up with reasonable clinical expectations.
   e. Etc

The reviewer does not intend to minimize the importance of any of these points; however, virtually no one would argue that: a) we should not be support subjects in home studies, b) short term inpatient pilot studies should not precede long-term home studies, c) the main goal of closed-loop therapy is to achieve good glycaemic control whilst reducing the risk of hypoglycaemia in people with type 1 diabetes, the main goal, or d) that unrealistic goals and expectations should be set. The reviewer would recommend removing anything for which there is already wide scale agreement and focusing the discussion on the more difficult questions on which there is not agreement. These could include questions as to what will the regulatory agencies require before allowing home studies (the FDA has guidance on this but this may differ in Europe), how good does the sensor need to be, what type of safety constraints need to be implemented, and others.
RESPONSE: The points are well taken. We modified the section taking into account the suggestions.

2. A number of studies of items are brought up for the first time rather late in the manuscript (sections analogous to discussion). The closed-loop studies by El-Kathib [ref 51], the use of amylin [52], faster acting insulin [53,54], and intraperitoneal insulin [55, 56].

RESPONSE: The ms has been modified appropriately.

REVIEWER 3 REPORT
Version: 1 Date: 20 September 2011
Reviewer: Claudio Cobelli

Major
This ms is superficial and incomplete to claim a review status. Important clinical and modelling & control studies are ignored. A more professional ms is needed to be considered for possible publication.

Specific
It is not clear why the authors discuss in some detail on pgg 6 & 7 Suspended Insulin Delivery given that the review is on closed-loop insulin delivery.

RESPONSE: Low glucose suspend is generally considered a “zero” generation close-loop insulin delivery system as insulin delivery is modulated (suspended) based on sensor glucose levels.