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Perspective on musculoskeletal modelling and predictive simulations of human movement to assess the neuromechanics of gait

Friedl De Groote and Antoine Falisse

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Original submission:	24 November 2020
Revised submission:	2 February 2021
Final acceptance:	2 February 2021

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSPB-2020-2432.R0 (Original submission)

Review form: Reviewer 1 (Ton van den Bogert)

Recommendation
Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Excellent

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
N/A

Is it clear?
N/A

Is it adequate?
N/A

Do you have any ethical concerns with this paper?
No

Comments to the Author
This manuscript presents an excellent review of the field of predictive simulation of human movement. The paper is well organized, well written, and very accessible to non-experts. It was a pleasure to read.

My only suggestion is to add to the description of open-loop vs. closed loop trajectory optimizations, which are both gaining popularity. Some additional information could help guide readers towards appropriate methods for their research questions.

The following points could be mentioned:

Potential benefits of control policy optimization:

(1) Open loop controlled models are usually unstable and require collocation methods to solve, leading to thousands of unknowns and constraints, hence the use of gradient-based optimization with the risk of not finding a global optimum. Control policy models optimize far fewer parameters (typically less than 100) and can be solved with shooting methods, allowing for the use of powerful unconstrained, derivative-free methods. Such methods are typically better at finding global optima and are also quite suitable for parallel computing.

(2) Solving for robust optimal control is quite straightforward, because random noise or obstacles can be added to each instance of the simulation. This does not increase computation time, and can be handled by the prevailing derivative-free optimization methods. This could also be mentioned in the Discussion section, under "robust optimal control". Robust optimal control is a very important direction for future work, so it may be good to mention this additional idea.
Some limitations of control policy optimization:

(1) In collocation methods, open-loop controls are typically represented by a control value for each actuator at each collocation point, allowing optimization of fine details in the control. In contrast, closed-loop controls are typically represented by less than 100 parameters, which limits the solution space to those trajectories that can be produced with the chosen controller architecture. While the human control system is certainly a feedback controller, it has a very large solution space. Therefore, control policy optimization may not find a solution that humans use, if it is outside of the solution space. Another consequence of this limitation is that the controller

architecture must be carefully designed for the movement task being investigated.

(2) In collocation methods, it is straightforward to add task constraints that enforce movement features such as periodicity, locomotion speed, or the final position of a reachign movement. With control policy optimization, this is not always possible. While periodicity is often an emergent feature of feedback-controlled systems (e.g. Geyer & Herr, 2010), other task constraints are difficult to enforce. For example, to see whether an assistive device or sport shoe decreases the metabolic cost of locomotion, optimizations need to be constrained to the same locomotion speed, exactly as in a treadmill experiment. So far, shooting methods have not had this capability.

Review form: Reviewer 2 (Marjolein van der Krogt)

Recommendation
Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

> **Is it accessible?**
> N/A
>
> **Is it clear?**
> N/A
>
> **Is it adequate?**
> N/A

Do you have any ethical concerns with this paper?
No

Comments to the Author
See attached file (Appendix A).

Decision letter (RSPB-2020-2432.R0)

26-Jan-2021

Dear Dr De Groote

I am pleased to inform you that your manuscript RSPB-2020-2432 entitled "Perspective on musculoskeletal modelling and predictive simulations of human movement to assess the neuromechanics of gait" has been accepted for publication in Proceedings B.

The referee(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the referee(s)' comments and revise your manuscript. Because the schedule for publication is very tight, it is a condition of publication that you submit the revised version of your manuscript within 7 days. If you do not think you will be able to meet this date please let us know.

To revise your manuscript, log into https://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, you will be able to respond to the comments made by the referee(s) and upload a file "Response to Referees". You can use this to document any changes you make to the original manuscript. We require a copy of the manuscript with revisions made since the previous version marked as ‘tracked changes’ to be included in the ‘response to referees’ document.

Before uploading your revised files please make sure that you have:

1) A text file of the manuscript (doc, txt, rtf or tex), including the references, tables (including captions) and figure captions. Please remove any tracked changes from the text before submission. PDF files are not an accepted format for the "Main Document".

2) A separate electronic file of each figure (tiff, EPS or print-quality PDF preferred). The format should be produced directly from original creation package, or original software format. PowerPoint files are not accepted.

3) Electronic supplementary material: this should be contained in a separate file and where possible, all ESM should be combined into a single file. All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

Online supplementary material will also carry the title and description provided during submission, so please ensure these are accurate and informative. Note that the Royal Society will not edit or typeset supplementary material and it will be hosted as provided. Please ensure that the supplementary material includes the paper details (authors, title, journal name, article DOI). Your article DOI will be 10.1098/rspb.[paper ID in form xxxx.xxxx e.g. 10.1098/rspb.2016.0049].

4) A media summary: a short non-technical summary (up to 100 words) of the key findings/importance of your manuscript.

5) Data accessibility section and data citation
It is a condition of publication that data supporting your paper are made available either in the electronic supplementary material or through an appropriate repository. Please see our Data Sharing Policies https://royalsociety.org/journals/authors/author-guidelines/#data.

In order to ensure effective and robust dissemination and appropriate credit to authors the dataset(s) used should be fully cited. To ensure archived data are available to readers, authors should include a 'data accessibility' section immediately after the acknowledgements section. This should list the database and accession number for all data from the article that has been made publicly available, for instance:
• DNA sequences: Genbank accessions F234391-F234402
• Phylogenetic data: TreeBASE accession number S9123
• Final DNA sequence assembly uploaded as online supplemental material
• Climate data and MaxEnt input files: Dryad doi:10.5521/dryad.12311
NB. From April 1 2013, peer reviewed articles based on research funded wholly or partly by RCUK must include, if applicable, a statement on how the underlying research materials – such as data, samples or models – can be accessed. This statement should be included in the data accessibility section.

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6) For more information on our Licence to Publish, Open Access, Cover images and Media summaries, please visit https://royalsociety.org/journals/authors/author-guidelines/.

Once again, thank you for submitting your manuscript to Proceedings B and I look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Sincerely,
Dr Locke Rowe
mailto: proceedingsb@royalsociety.org

Associate Editor
Board Member: 1
Comments to Author:
Dear Authors,
Both reviewers provide positive assessments of your review paper. Congratulations. In doing so, they provide useful conceptual and specific, more detailed comments for revising your paper to improve its clarity, scope and overall message. This relates to clarifying the benefits and challenges of open-loop vs closed-loop simulations, as well as for restructuring how you organize your paper by using subheadings to guide the reader. The suggestion to conclude with a broader future perspective, rather than cast as limitations and strengths of simulation approaches also seems a good one to consider.

Reviewer(s)' Comments to Author:
Referee: 1
Comments to the Author(s)
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(2) Solving for robust optimal control is quite straightforward, because random noise or obstacles can be added to each instance of the simulation. This does not increase computation time, and can be handled by the prevailing derivative-free optimization methods. This could also be mentioned in the Discussion section, under “robust optimal control”. Robust optimal control is a very important direction for future work, so it may be good to mention this additional idea.

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Referee: 2
Comments to the Author(s)
See attached file

Author's Response to Decision Letter for (RSPB-2020-2432.R0)

See Appendix B.

Decision letter (RSPB-2020-2432.R1)

02-Feb-2021

Dear Dr De Groote

I am pleased to inform you that your manuscript entitled "Perspective on musculoskeletal modelling and predictive simulations of human movement to assess the neuromechanics of gait" has been accepted for publication in Proceedings B.

You can expect to receive a proof of your article from our Production office in due course, please check your spam filter if you do not receive it. PLEASE NOTE: you will be given the exact page length of your paper which may be different from the estimation from Editorial and you may be asked to reduce your paper if it goes over the 10 page limit.

If you are likely to be away from e-mail contact please let us know. Due to rapid publication and an extremely tight schedule, if comments are not received, we may publish the paper as it stands.

If you have any queries regarding the production of your final article or the publication date please contact procb_proofs@royalsociety.org

Your article has been estimated as being 10 pages long. Our Production Office will be able to confirm the exact length at proof stage.

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All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

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Thank you for your fine contribution. On behalf of the Editors of the Proceedings B, we look forward to your continued contributions to the Journal.

Sincerely,
Editor, Proceedings B
mailto: proceedingsb@royalsociety.org

Appendix A

This paper gives an overview of recent advances in the field of predictive simulations of gait, describing different methods applied, key insights gained, as well limitations and future recommendations. The paper is a quite complete and a useful overview for researchers in this field, as well as people new to the area of predictive simulation.

I have several recommendations that can be considered by the authors to further improve the clarity of the paper.

General comments

- The different headings and subheadings could be phrased more logically, to better cover the contents. More specifically, I would propose headings like 'Simulation approaches' or the like (rather than 'Review'), followed by 'Key insights from predictive simulation studies' (rather than a separate sentence, saying 'below we summarize key insights …'; followed with subheadings with the specific topics of these key insights. Finally, a section named something like 'Limitations and future perspectives' rather than the general 'Discussion' would better cover the contents and guide the reader.
- In the discussion section, I would appreciate to see a bit more focus on future perspective and concrete recommendations for research, rather than a description of limitations and issues. This is merely a matter of wording used (positive phrasing rather than negative) and relates to the general tone, not all parts of the discussion.

More specific comments:

- Page 3, after first paragraph (… open questions.) I would expect a transition to a description of the more complex models, while the next paragraph describes conceptual models first. This passage could be more fluent.
- Page 4, last sentence 1st paragraph, and 1st sentence of 2nd paragraph seem a bit redundant
- Page 4, paragraph about complex models is lengthy and relatively difficult to read; could benefit from a more explicit structure (first, second, third, etc), listing the important aspects of such complex models. Furthermore, an example for sprinting is given to explain the relevance of 3D models, which seems out of place.
- Figure 2, shouldn't there also be a feedback loop from movement back to the CNS, as often the state of the model (kinematics, ground contacts etc) is used as input for the controller?
- Page 6: "They used a direct shooting approach combined with a simulated annealing algorithm to solve the underlying optimal control problem. The adoption of direct collocation methods, instead of shooting methods, together with gradient descent algorithms, e.g., IPOPT (20), has helped reduce computational time." -> short explanation of difference between these approaches/why direct collocation is faster would make it informative for a wider public.
- Page 6 "In 2019, Geijtenbeek et al. published SCONE, an open-source software package to generate predictive simulations that builds on the work of Wang et al. (18)." Seems not completely true, as SCONE is not just based on Wang et al., but allows using various control strategies for a range of tasks, including (but not limited to) the work of Wang et al, Geyer & Herr, etc.
- Page 6, part about reinforcement learning could be better clarified; it is also not particularly clear to me how it relates to the previous
- Page 7, 'Both approaches', would be useful to repeat the names here for clarity

- Page 7-11 (throughout section on key insights); make sure to list not only the studies' results but also the relevance (key insights); this is often done but not always
- Page 7 "However, we feel that further efforts are needed to validate"→ move to recommendations section?
- Page 7 "Yet such complexity is required to unveil gait control strategies as well as compensation strategies due to neuro-musculoskeletal deficits." -> 2D may be enough if interested in strategies in sagittal plane only? And none of examples explains why a redundant set of muscles is required?
- Tracking simulations are mentioned several times throughout the paper (especially in part on key insights), but the description of these is often not complete (not all literature on tracking simulations regarding these topics is listed), and also seems out of scope of this paper. Consider to remove these parts altogether.
- Page 8, 'inverse optimal control', this method is not introduced in the first part that I consider the 'methods' section (or: simulation approaches). Would be useful to cover this in this part as well (or remove completely if out of scope).
- Page 8, 'Feasibility of gait control architectures', introduce better the meaning and relevance of this topic
- Page 9 "Based on a 3D muscle-driven model, Song and Geyer showed that muscular changes, i.e., loss of muscle strength and mass, rather than neural changes, i.e., slower neural conduction speed and sensorimotor noise, are at the origin of reduced walking economy and speed in older adults (46)." → 'rather than' may be stated too strongly; as this paper states: "we find evidence that the loss of muscle strength and muscle contraction speed *dominantly* contribute to the reduced walking economy and speed."
- Page 10, description of paper 48: only the limitations of this study's methods are described, not the key insights this study (albeit simple) has yielded.
- Page 12, "We might take inspiration from motor control models that have been used to simulate animal locomotion (e.g., (57)(58)).", Interesting topic, please extend on this, give examples/ideas?
- Page 12 "will require us'', rephrase 'us' to make general for the community (as 'we' is used throughout for own studies). Idem page 14, 'We have little insight'.
- Page 12-13 'Optimality principles' this paragraph could benefit from some further explanation or more specific examples, for instance of 'experimental conditions' etc.
- Page 13 'our recent work shows' → add reference?
- Page 13, last sentence 'of more complex models' → add *and realistic* (just more complex is not always better)

Appendix B

Response to the reviewer's comments

Both reviewers provide positive assessments of your review paper. Congratulations. In doing so, they provide useful conceptual and specific, more detailed comments for revising your paper to improve its clarity, scope and overall message. This relates to clarifying the benefits and challenges of open-loop vs closed-loop simulations, as well as for restructuring how you organize your paper by using subheadings to guide the reader. The suggestion to conclude with a broader future perspective, rather than cast as limitations and strengths of simulation approaches also seems a good one to consider.

The reviewers' suggestions were very helpful to further improve our paper. Below, we describe how we addressed each comment/suggestion.

Referee: 1

Comments to the Author(s)
This manuscript presents an excellent review of the field of predictive simulation of human movement. The paper is well organized, well written, and very accessible to non-experts. It was a pleasure to read.

Thank you.

My only suggestion is to add to the description of open-loop vs. closed loop trajectory optimizations, which are both gaining popularity. Some additional information could help guide readers towards appropriate methods for their research questions.

We agree with this suggestion and have added additional information (for details, see response to the following comments).

The following points could be mentioned:

Potential benefits of control policy optimization:

(1) Open loop controlled models are usually unstable and require collocation methods to solve, leading to thousands of unknowns and constraints, hence the use of gradient-based optimization with the risk of not finding a global optimum. Control policy models optimize far fewer parameters (typically less than 100) and can be solved with shooting methods, allowing for the use of powerful unconstrained, derivative-free methods. Such methods are typically better at finding global optima and are also quite suitable for parallel computing.

We now mention that direct collocation results in large non-linear programming problems and is especially beneficial for unstable dynamics:

"The adoption of direct collocation methods, instead of shooting methods, has helped reduce computational time. In shooting methods, the dynamics are integrated over the time horizon of the simulation based on the current guess of the controls to obtain the states required to evaluate the cost function and constraints. In collocation methods, the discretized states and controls are optimization variables and the integration scheme is expressed by a set of

constraints that is solved simultaneously with minimizing the cost function. The resulting large-scale nonlinear programming problems (NLP) are sparse and can be efficiently solved using gradient descent algorithms, e.g., IPOPT (20). Compared to direct shooting, direct collocation reduces the sensitivity of the objective function to the optimization variables by reducing the time horizon of the integration. Hence, collocation methods are especially beneficial to solve problems with unstable dynamics, such as open-loop musculoskeletal dynamics of bipedal locomotion."

Indeed, gradient-based optimization methods return a local optimum, which might not be the global optimum. It is however unclear whether shooting combined with derivative-free optimization methods is better than direct collocation combined with gradient-based optimization methods at finding global optima when simulating gait. As far as we know, there are no direct comparisons between methods for simulations of walking. This lack of direct comparisons might be explained by different methods being more suitable for trajectory versus control policy optimization as pointed out by the reviewer. In many studies, derivative free methods were stopped after a predefined number of iterations (without the optimality conditions being guaranteed to be fulfilled). Also, derivative free methods are often started from different initial populations and the most optimal solution is selected (e.g., Ong et al. 2019, Ong et al. 2016, and Song & Geyer 2015), which suggests that the global optimum is not always found. Also, not only the optimization method but also the problem formulation might influence which local optimum is found (see, e.g. *Convex Optimization* by Boyd and Vandenberghe). We therefore chose to not include any strong statements on shooting combined with derivative free methods being better at finding global optima.

Derivative-free methods are indeed suitable for parallel computing. Similarly, function evaluations can be parallelized when using direct collocation. However, in our simulations of human gait, the CPU time spent in function evaluations is much less than the time spent in the solver, partly thanks to the use of AD (reverse mode), and hence the bottleneck in terms of CPU time is the solver. Parallel computing might be more beneficial when not using AD, where a larger part of the total CPU time is spent in evaluating the NLP functions. Also here, we chose to not make any strong statements in the manuscript.

(2) Solving for robust optimal control is quite straightforward, because random noise or obstacles can be added to each instance of the simulation. This does not increase computation time, and can be handled by the prevailing derivative-free optimization methods. This could also be mentioned in the Discussion section, under "robust optimal control". Robust optimal control is a very important direction for future work, so it may be good to mention this additional idea.

Thank you for pointing this out. We rewrote the subsection on robust optimal control.

"*Todorov and Jordan demonstrated that it was important to account for uncertainty when optimizing task performance to realistically reproduce upper limb movements (63) but uncertainty, e.g., due to sensorimotor noise, is often neglected when simulating gait. When using shooting methods to compute control policies, accounting for uncertainty is computationally straightforward because sensorimotor and external noise can be added when evaluating the dynamics. Yet the high computational cost of current computational approaches for control policy optimization might be a barrier to applying stochastic optimal* *control to complex models. Since robustness against uncertainty requires feedback control, trajectory optimization is by design unsuited for studying stochastic optimal control. Future methodological developments should therefore aim at leveraging the recent computational advances that improved the efficiency of trajectory optimization to stochastic optimal control. For example, Koelewijn and van den Bogert accounted for control noise when simulating walking based on a torque-driven sagittal plane model (64). They computed open loop controls and gains of reflexive joint controllers by optimizing performance over a set of predefined noise trajectories using direct collocation and gradient-based optimization. Increased control noise resulted in larger foot clearance. We are currently exploring whether the approach suggested by Houska et al. for mechatronic control (65) is applicable to simulate human gait. The main idea is to approximate the stochastic state by its mean and covariance, and to approximate the dynamics of the state covariance using the continuous Lyaponuv equation. The resulting approximate deterministic optimal control problem can then be solved with direct collocation. However, it remains to be seen whether computational efficiency can be improved using such approaches given the large size of the resulting optimal control problems.*"

Some limitations of control policy optimization:

(1) In collocation methods, open-loop controls are typically represented by a control value for each actuator at each collocation point, allowing optimization of fine details in the control. In contrast, closed-loop controls are typically represented by less than 100 parameters, which limits the solution space to those trajectories that can be produced with the chosen controller architecture. While the human control system is certainly a feedback controller, it has a very large solution space. Therefore, control policy optimization may not find a solution that humans use, if it is outside of the solution space. Another consequence of this limitation is that the controller architecture must be carefully designed for the movement task being investigated.

We fully agree and discuss this in the subsection on Motor control models within the section on Challenges and future perspectives:

Approaches that predict human walking by computing optimal control policies have mainly relied on reflex-based controllers. Reflex pathways implemented in popular models are simplifications of the reflex system and only part of the muscle input can likely be attributed to reflexes (56). Reflex models have been extended by central pattern generators (41) and supraspinal inputs (31), yet none of these simple control models captures the complexity of human motor control.

(2) In collocation methods, it is straightforward to add task constraints that enforce movement features such as periodicity, locomotion speed, or the final position of a reaching movement. With control policy optimization, this is not always possible. While periodicity is often an emergent feature of feedback-controlled systems (e.g. Geyer & Herr, 2010), other task constraints are difficult to enforce. For example, to see whether an assistive device or sport shoe decreases the metabolic cost of locomotion, optimizations need to be constrained to the same locomotion speed, exactly as in a treadmill experiment. So far, shooting methods have not had this capability.

We agree that it is useful to point out that gradient-based optimization methods allow for easy inclusion of constraints, which is less straightforward with derivative free methods. We added the following sentence to the paragraph on control policy optimization:

"In addition, computational approaches for control policy optimization are typically less suitable for dealing with task constraints, such as periodicity or locomotion speed, than computational approaches for trajectory optimization."

This paper gives an overview of recent advances in the field of predictive simulations of gait, describing different methods applied, key insights gained, as well limitations and future recommendations. The paper is a quite complete and a useful overview for researchers in this field, as well as people new to the area of predictive simulation.

Thank you for the positive comment.

I have several recommendations that can be considered by the authors to further improve the clarity of the paper.

General comments

The different headings and subheadings could be phrased more logically, to better cover the contents. More specifically, I would propose headings like 'Simulation approaches' or the like (rather than 'Review'), followed by 'Key insights from predictive simulation studies' (rather than a separate sentence, saying 'below we summarize key insights …'; followed with subheadings with the specific topics of these key insights. Finally, a section named something like 'Limitations and future perspectives' rather than the general 'Discussion' would better cover the contents and guide the reader.

We edited the headings following the reviewer's suggestion.

In the discussion section, I would appreciate to see a bit more focus on future perspective and concrete recommendations for research, rather than a description of limitations and issues. This is merely a matter of wording used (positive phrasing rather than negative) and relates to the general tone, not all parts of the discussion.

We edited the wording in the Challenges and future perspectives section.

More specific comments:

Page 3, after first paragraph (… open questions.) I would expect a transition to a description of the more complex models, while the next paragraph describes conceptual models first. This passage could be more fluent.

We aimed to give an overview in the first paragraph. We agree that as a result we jump back and forth between conceptual and complex models, but we prefer to already introduce both model types before providing more details.

Page 4, last sentence 1st paragraph, and 1st sentence of 2nd paragraph seem a bit redundant

We agree that there is some overlap between these sentences, yet we find it important to have a conclusive sentence at the end of the paragraph and therefore we decided to keep it.

Page 4, paragraph about complex models is lengthy and relatively difficult to read; could benefit from a more explicit structure (first, second, third, etc), listing the important aspects of such complex models. Furthermore, an example for sprinting is given to explain the relevance of 3D models, which seems out of place.

We added more structure:

"Complex models might elucidate how the neuro-musculoskeletal system realizes gait principles identified through conceptual models. Here, we consider a model complex when it represents multiple lower limb segments and joints driven by a redundant set of muscle-tendon actuators with dynamics inspired by muscle physiology. ***First****, taking the complex, three-dimensional (3D), musculoskeletal geometry into account is important to understand both pathological gait and athletic performance. For example, patients with weak hip abductors adopt a Trendelenburg gait pattern with compensations in both the frontal and sagittal planes and sprinters have been shown to have smaller Achilles tendon moment arms and longer toes than non-sprinters (11).* ***Second****, accurately modelling muscle-tendon actuators is important to understand movement economy. Muscle dynamics are closely linked to muscle energetics with muscle force being produced at lower metabolic rates when a muscle works isometrically close to its optimal length (12). Interactions between muscles and tendons influence muscle efficiency by altering the muscles' operating length and velocity and by allowing for storage and release of energy in the tendons.* ***Third****, accurately modelling the musculoskeletal system is also crucial to study its interaction with the neural system. The intrinsic mechanical properties of the musculoskeletal system, especially muscles, provide stability against external perturbations, thereby reducing the need for active control (e.g., (13)).* ***Finally****, studying how muscles are coordinated by the neural system requires models driven by a redundant set of muscles."*

We did not limit ourselves to walking and therefore think that the sprinting example is relevant.

Figure 2, shouldn't there also be a feedback loop from movement back to the CNS, as often the state of the model (kinematics, ground contacts etc) is used as input for the controller?

Yes, we added it.

Page 6: "They used a direct shooting approach combined with a simulated annealing algorithm to solve the underlying optimal control problem. The adoption of direct collocation methods, instead of shooting methods, together with gradient descent algorithms, e.g., IPOPT (20), has helped reduce computational time." -> short explanation of difference between these approaches/why direct collocation is faster would make it informative for a wider public.

As suggested by the reviewer, we have added a short explanation of the main differences between single shooting and direct collocation:

"The adoption of direct collocation methods, instead of shooting methods, has helped reduce computational time. In shooting methods, the dynamics are integrated over the time horizon of the simulation based on the current guess of the controls to obtain the states required to evaluate the cost function and constraints. In collocation methods, the discretized states and controls are optimization variables and the integration scheme is expressed by a set of constraints that is solved simultaneously with minimizing the cost function. The resulting large-scale nonlinear programming problems (NLP) are sparse and can be efficiently solved using gradient descent algorithms, e.g., IPOPT (20). Compared to direct shooting, direct collocation reduces the sensitivity of the objective function to the optimization variables by reducing the time horizon of the integration. Hence, collocation methods are especially beneficial to solve problems with unstable dynamics, such as open-loop musculoskeletal dynamics of bipedal locomotion."

Page 6 "In 2019, Geijtenbeek et al. published SCONE, an open-source software package to generate predictive simulations that builds on the work of Wang et al. (18)." Seems not completely true, as SCONE is not just based on Wang et al., but allows using various control strategies for a range of tasks, including (but not limited to) the work of Wang et al, Geyer & Herr, etc.

We agree that SCONE is not just based on Wang et al. We meant to say that SCONE uses similar methods as the ones used by Wang et al. We have adjusted our statement to reflect that better:

"In 2019, Geijtenbeek et al. published SCONE, an open-source software package to generate predictive simulations by computing control policies using covariance matrix adaptation."

Page 6, part about reinforcement learning could be better clarified; it is also not particularly clear to me how it relates to the previous

We added a sentence to improve the flow:

"In 2019, Geijtenbeek et al. published SCONE, an open-source software package to generate predictive simulations by computing control policies using covariance matrix adaptation (18). ***Alternatively, reinforcement learning has been used to solve for control policies.*** *Since 2017, the NeurIPS "Learn to move" competition series has accelerated the adoption of reinforcement learning techniques to simulate human locomotion based on neuro-musculoskeletal models (for detailed reviews, see (28) and (29))."*

Page 7, 'Both approaches', would be useful to repeat the names here for clarity

Edit made: "***Both trajectory optimization and approaches that solve for gait control policies*** *generated simulations that capture key features of human gait."*

Page 7-11 (throughout section on key insights); make sure to list not only the studies' results but also the relevance (key insights); this is often done but not always

We added key insights where they were lacking.

Page 7 "However, we feel that further efforts are needed to validate" move to recommendations section?

We did not follow this suggestion as we felt it was more clear to keep this paragraph together.

Page 7 "Yet such complexity is required to unveil gait control strategies as well as compensation strategies due to neuro-musculoskeletal deficits." -> 2D may be enough if interested in strategies in sagittal plane only? And none of examples explains why a redundant set of muscles is required?

We agree that 2D simulations might give useful insights in sagittal plane strategies but control of movement in different planes is coupled and therefore 3D simulations might yield additional insight even in sagittal plane strategies. Also, simulations cannot give insight in how a redundant set of muscles is controlled if this redundancy is not modeled. We edited the text to clarify this further:

*"Relatively few studies have used 3D models with a redundant set of muscles. Yet, given that control of movement is realized through a redundant set of muscles and is coupled between planes, such complexity is required to unveil gait control strategies as well as compensation strategies due to neuro-musculoskeletal deficits.***"**

We believe that the first example, i.e., the optimality criterion that results in a realistic gait pattern depends on the model used, covers both the need for 3D models and a redundant set of muscles. We edited the text to better reflect this:

"For instance, we observed that we needed to minimize metabolic energy rate squared in addition to muscle activities squared when simulating walking based on a 3D model ***with a redundant set of muscles*** *to prevent excessive trunk sway in the frontal plane (3), whereas others have obtained realistic sagittal plane gait patterns by minimizing only activations squared based on a 2D model* ***in which groups of agonistic mono- and bi-articular actuators were represented by single muscles*** *(21)."*

We did not separately test the effects of increasing the dimensions (2D to 3D) and increasing the number of muscles in predictive simulations of human gait but it is likely that both contributed to the differences in observations. In particular, inverse dynamic simulations have demonstrated that the number of muscle-tendon actuators influences the force distribution given the same optimization criterion and that minimizing activations squared results in a more equal distribution over agonistic muscles than minimizing metabolic cost (Zargham et al., *J. Biomech.*, 2019). We could not address this in more detail in the manuscript due to the word limit.

Tracking simulations are mentioned several times throughout the paper (especially in part on key insights), but the description of these is often not complete (not all literature on tracking simulations regarding these topics is listed), and also seems out of scope of this paper. Consider to remove these parts altogether.

We indeed did not cover all literature on tracking simulations, we only included example studies that looked at related topics. We agree that tracking simulations are out of scope and followed the reviewer's suggestion to remove parts on tracking simulations. We only kept one tracking study on gait retraining from Fregly et al. as it contained the original idea that was elaborated in future predictive simulations studies and we therefore considered it very relevant for the topic being discussed.

Page 8, 'inverse optimal control', this method is not introduced in the first part that I consider the 'methods' section (or: simulation approaches). Would be useful to cover this in this part as well (or remove completely if out of scope).

Since inverse optimal control is specifically used to study optimality principles underlying gait control - as opposed to being common to multiple applications - we decided to leave it in the section on 'Optimality principles underlying gait control'. We feel it is within the scope of our perspective as predictive simulations rely heavily on the assumption of optimal control.

Page 8, 'Feasibility of gait control architectures', introduce better the meaning and relevance of this topic

We edited the text to better introduce this topic:

"Simulations have helped elicit the role of control structures, such as reflexes and central pattern generators, in generating stable and versatile walking patterns. By simulating control architectures, often inspired by experimental observations, researchers have tested their ability to generate human-like walking."

Page 9 "Based on a 3D muscle-driven model, Song and Geyer showed that muscular changes, i.e., loss of muscle strength and mass, rather than neural changes, i.e., slower neural conduction speed and sensorimotor noise, are at the origin of reduced walking economy and speed in older adults (46)." 'rather than' may be stated too strongly; as this paper states: "we find evidence that the loss of muscle strength and muscle contraction speed dominantly contribute to the reduced walking economy and speed."

We rephrased:

"Based on a 3D muscle-driven model, Song and Geyer showed that muscular changes, i.e., loss of muscle strength and mass, contribute more to reduced walking economy and speed in older adults than neural changes, i.e., slower neural conduction speed and sensorimotor noise (46)."

Page 10, description of paper 48: only the limitations of this study's methods are described, not the key insights this study (albeit simple) has yielded.

We also described which gait modifications were identified to reduce knee adduction moment, which to us is the key insight of this paper. We edited the text, hoping to better communicate this.

"Fregly et al. used simulations based on a 3D torque-driven model to design gait modifications that reduced the knee adduction moment while minimizing deviations from the patient's self-selected kinematics (48). They found that slightly increasing leg flexion, decreasing pelvic obliquity and increasing pelvic axial rotation decreased the knee adduction moment."

Page 12, "We might take inspiration from motor control models that have been used to simulate animal locomotion (e.g., (57)(58)).", Interesting topic, please extend on this, give examples/ideas?

The reader is referred to the reference as the word limit did not allow us to expand.

Page 12 "will require us'', rephrase 'us' to make general for the community (as 'we' is used throughout for own studies). Idem page 14, 'We have little insight'.

We made the following edits:
will require us to embed ... -> ***will require embedding ...***
We have little insight into … -> ***Insight into … is limited.***

Page 12-13 'Optimality principles' this paragraph could benefit from some further explanation or more specific examples, for instance of 'experimental conditions' etc.

We added specific examples of experimental conditions:

"While trade-offs between criteria might be subtle for steady-state level-ground walking, they might be more pronounced in other conditions (62). Predictive simulations could help identify experimental conditions that would allow distinguishing between optimality criteria. ***For example, simulations could be used to explore the mechanical constraints (e.g., limited joint range of motion or foot-ground contact locations, slopes or stairs, added segment mass or volume) that lead to the largest predicted difference in kinematics when prioritizing minimizing metabolic cost versus muscle activity squared, which might be a measure of fatigue.****"*

Page 13 'our recent work shows' add reference? Page 13, last sentence 'of more complex models' add *and realistic* (just more complex is not always better)

Unfortunately, this work has not yet been published. We re-phrased that sentence to clarify that there is no associated publication:

"whereas in recent work we found that it has a large effect on the knee torque in predictive simulations (unpublished)."

We added realistic:

We think that computational speed is an important limitation to the adoption of more complex ***and realistic*** *models of muscle dynamics.*