

Review of Doctoral Thesis

1. PhD candidate
Ing. David Rebenda / david.rebenda@vut.cz
2. Name of PhD programme
Design and Process Engineering (Mechanical Engineering Design)
3. Title of PhD thesis
Effect of Viscosupplementation on Friction of Articular Cartilage
4. Principal supervisor
doc. Ing. Martin Vrbka, Ph.D. / martin.vrbka@vut.cz
5. Co-supervisor
Ing. David Nečas, Ph.D. / david.necas@vut.cz
6. Reviewer
Prof. Yoshinori Sawae / sawa@mech.kyushu-u.ac.jp
Department of Mechanical Engineering, Faculty of Engineering, Kyushu University
7. Overview of the scope of PhD thesis¹
Very good
Justification for evaluation: 100 – 200 words. Motivation and purpose of the dissertation thesis are clearly defined based on practical needs in the orthopedic field and research hypotheses are established based on the intensive review of relevant literatures. Experimental plans are carefully organized to verify research hypotheses by referring several previous studies. They are mostly reasonable to obtain necessary experimental data about rheological characteristics of HA solutions and viscosupplements in addition to their impacts on the frictional behavior of articular cartilage. Significant amounts of experimental results have been accumulated to deliver some valuable insights related to the research target of this thesis. The above-mentioned information is well summarized in Abstract and Conclusions.
8. Significance of the topic and clarity of problem statement
Excellent
Justification for evaluation: 100 – 200 words. This study aims to characterize rheological properties of HA solutions and commercial viscosupplements (VSs) and to evaluate their effects on frictional behavior of articular cartilage. It is perfectly matched with a strong

¹ Overview of the scope of PhD thesis is a short description of objectives of PhD thesis's research and summary of main findings and scientific achievements.

demand for scientific researches in the aged modern society. HA-based VSs have been used preferably in a palliative treatment for the early stage of osteoarthritis and their demand is now continuously increasing worldwide with a progress of aging in the society. However, many uncertainties are still remained in the background mechanisms of physiological effects caused by VSs. Research outcomes from this study are expected to contribute to better understanding of therapeutic effects of viscosupplementation and improvement of its effectiveness. In addition, research hypotheses are appropriately formulated based on careful analyses of previous studies. They are mostly reasonable and consistent with the research motivation.

9. Knowledge of existing literature

Very good

Justification for evaluation: 100 – 200 words. A wide range of literatures related to the synovial joint lubrication has been reviewed and certain amount of relevant knowledge has been accumulated. Especially, an extensive correction of rheological data of healthy and pathological synovial fluids is impressive. However, some important references for the boundary lubrication mechanism by synovial fluid constituents are missing from the literature review in Chapter 2 and the literature list in Pages 114 to 118, for example Hills and Buttler 1984, Higaki et al. 1998 (even though they appeared in reference list of attached manuscripts). Research on the boundary lubrication effect of HA and lubricin has a long history and following classic literatures are worth including in the literature review to deepen the knowledge about them. 1) A.G. Ogston, J.E. Stanier, J Physiol, 119, 244-252 (1953). 2) E.L. Radin, D.A. Swann, Nature, 228, 377-378 (1970). 3) D.A. Swann, et al., J Biol Chem, 256, 5921-5925 (1981). 4) D.A. Swann, et al., Arthritis Rheum, 24, 22-30 (1981). 5) B.L. Schumacher, et al., Arch Biochem Biophys, 311, 144-152 (1994). 6) S.G. Rees, et al., Matrix boil, 21, 593-602 (2002). In addition, certain literatures about hydrated hydrogel friction would be useful to understand the frictional behavior of PVA hydrogel.

10. Choice of methods and technical soundness

Good

Justification for evaluation: 100 – 200 words. In this study, rheological properties of HA solutions, VSs and model synovial fluid supplemented with VS were explored by using two types of rotational rheometer. The most suitable combination of rheometer and measurement set up was carefully selected for each measurement; HR-3 with cone-plate set up was used for the steady shear test to measure shear rate-dependent viscosity and AR-G2 with parallel plates was chosen for the oscillatory test to obtain viscoelastic properties. The appropriate selection of experimental set up contributed the successful high-accuracy measurements of rheological properties. Friction of cartilage specimens were measured by utilizing a commercially available friction tester. The specimen setting and experimental conditions were decided by referring successful previous studies. However, more discussions about the relevance of whole experimental procedure and test conditions of friction measurement would be necessary, since repeatability of friction measurements in this study was certainly insufficient. Especially, some questions are remained about preparation and storage method of cartilage specimens.

11. Quality, originality and significance of the results
Good
Justification for evaluation: 100 – 200 words. Rheological data of VSs and model synovial fluids supplemented with VS obtained in this study have enough novelty and certain scientific values. They filled a remained vacancy in the knowledge about rheological characteristics of VSs and physical influences of viscosupplementation as the medical treatment. Also, prospective friction reduction effects of VSs in synovial joints could be estimated by using PVA hydrogel as a model of hydrated articular cartilage tissue. In addition, certain difference in the friction reduction effect could be confirmed among 5 VSs. It is also a valuable achievement of this study. Experimental results obtained in this study might provide some logical background for the selection of VSs to orthopedic surgeons.
12. Quality of attached papers
Good
Justification for evaluation: 100 – 200 words. The first paper contains results of comprehensive friction measurements for fresh cartilage specimens with 13 different lubricants and effects of synovial fluid compositions have been discussed. Overall structure of the manuscript is well organized. A large number of experimental results were systematically summarized and subsequently the importance of interaction of globulin, HA and PHs was emerged. The second paper intended to clarify the relationship between rheological properties and lubrication effects of HA solutions. However, sufficient repeatability of friction measurements could not be obtained and it made conclusions of this study relatively weak. In the third paper, rheological properties of 5 VSs were intensively studied and clearly demonstrated their differences in shear rate-dependent viscosity and viscoelastic properties. It also contains clear friction test results which contributed to elicit firm conclusions.
13. Overall assessment, strengths and weaknesses (based upon the above evaluation categories 8–12)
Very good
Justification for evaluation: 100 – 200 words. Overall, the manuscript has enough novelty and scientific impacts as a dissertation thesis of PhD study. The major strength of this thesis is a significant accumulation of experimental data. Especially, experimental data of the shear rate-dependent viscosity and viscoelastic properties of HA solutions and VSs obtained in this study can be utilized in future studies about the synovial joint lubrication and medical treatments for osteoarthritis. The manuscript still has a clear weakness in the methodology of the friction measurement for natural articular cartilage. It results in relatively large scatter of COF and subsequently makes conclusions about the influence of VSs on cartilage friction relatively weak.
14. Questions and comments
1. Do you think the specimen configuration with a stable cartilage pin on a moving glass plate is best for evaluating the frictional behavior of articular cartilage? Have you tried to use another specimen configuration or much wider range of test condition in sliding tests to

improve the repeatability of friction measurement? 2. Have you examined effects of the preparation procedure and the storage method of cartilage specimens on results of the friction test? 3. More detailed discussion is necessary to justify the relevance of PVA hydrogen as a cartilage tissue model based on comparison of physical properties between PVA hydrogel and articular cartilage tissue, since results obtained with PVA hydrogel were completely different from frictional behavior of actual cartilage tissue in the second attached paper.

15. Conclusion

PhD thesis is an independent scientific work that presents a novel solution to a significant problem in the research area and demonstrates the candidate's ability to conduct independent research.

YES

16. Date and signature

30/07/2021

Please note

- A. Evaluate categories 7 to 13 using the following scale: unacceptable, acceptable, satisfactory, good, very good, excellent. The qualification of 'excellent' should only be given for a PhD Thesis in the top 3% of the research in your field of expertise.
- B. E-mail the completed form to: Klara.Javorcekkova@vut.cz

Review of Doctoral Thesis

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6. Reviewer
Axel C Moore, PhD, / axel.moore@imperial.ac.uk
Imperial College London
7. Overview of the scope of PhD thesis¹
Very good
The thesis reviews the state of the art in viscosupplementation which to date has been mainly a rheological characterization. In this work the candidate combines rheological analysis with tribological measures of cartilage against glass, PVA hydrogel against glass, and several commercial viscosupplements. The study design is good and the results are presented in a generally clear and appropriate manner. While effects of composition, concentration, Mw, speed, load, etc showed some effect, most were quite small and so it is worth asking if viscosupplements act through a mechano-tribological mechanism or another mode. Particularly, the candidate should think about the potential biochemical effects or immune modulation properties of these viscosupplements.
8. Significance of the topic and clarity of problem statement
Very good
Viscosupplementation is a strongly debated topic in the orthopaedics community and is of great importance to the field. As the thesis states, there are conflicting guidance from professional medical societies regarding its use. In general, viscosupplementation is a safe practice, minimally invasive, and may offer benefit if even through placebo effect. It would be good for the candidate to discuss the duration

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of repair from viscosupplementation and how this compares to phosphate buffered saline injections which have shown improvements out to 6 months and platelet rich plasma. One suggestion for the thesis is to make the link clearer that the candidate is aiming to link rheological performance with tribological. While this should work in the context of fluid film lubrication it should have little dependence on other modes and this appears to be the finding in this work. I would like to hear more discussion around what the findings tell us about the lubrication modes of cartilage.

9. Knowledge of existing literature

Good

The candidate has demonstrated a good knowledge of the literature throughout the thesis. This is demonstrated by a good range of citations and references of prior art. However, the thesis does not provide a deep understanding of the multitude of lubrication theories proposed for cartilage, rather it gives an overview. It would be good for the candidate to identify the lubrication modes that the results directly support or refute and give some detailed analysis. As a matter of personal interest, I would like to hear the candidate discuss their thoughts on how tribological rehydration may have played a role.

10. Choice of methods and technical soundness

Good

The data are presented well and information can be generally understood by just looking at the figures and captions. The candidate did well at maintaining consistent methods across multiple studies. I am unsure how the candidate selected certain testing conditions as no references or analysis was provided. For example, the sliding speeds used, the duration of sliding, the point at which friction was measured. If these values were based on some version of a scaled day, contact stress, etc it would be good to know. Several figures would have benefited from some supplemental plots that show the temporal data. Bar charts are great for summarizing the data but these temporal studies can be so rich with information.

11. Quality, originality and significance of the results

Good

The candidate has performed high quality work with originality and is important to the field of orthopaedics, tribology, and rheology. Specifically, the combination of tribology and rheology for viscosupplements is certainly an understudied problem and this work helps to address some of the current questions. While the results don't demonstrate wildly unexpected results the studies are well formulated and ask appropriate questions. It was mentioned several times in the thesis that repeatability was an issue with biological specimens however only average responses were shown without error bars or individual data points. Knowledge of this scatter would help in understanding the potential clinical significance of the results.

12. Quality of attached papers

Good

The attached papers are good examples of published work that provide both important technical information, methods, and results.

13. Overall assessment, strengths and weaknesses (based upon the above evaluation categories 8–12)



**INSTITUTE OF MACHINE
AND INDUSTRIAL DESIGN**



**Faculty of Mechanical Engineering
Brno University of Technology**

Evaluate:

Overall, the candidate has done very good work that merits the title of PhD. The main strengths of this work are clear and consistent methods, simple but good studies, and clear presentation of the findings. The main weaknesses are the lack of an in-depth analysis on what this means to the actual lubrication of cartilage (which lubrication theories are correct/wrong/most likely), what this means for wear (only friction and rheology were discussed), what this means in terms of the clinical outcomes and how we can improve viscosupplementation or alternative methods.

14. Questions and comments

None at this time.

15. Conclusion

PhD thesis is an independent scientific work that presents a novel solution to a significant problem in the research area and demonstrates the candidate's ability to conduct independent research.

YES

Principal supervisor's final report on the PhD study

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Effect of Viscosupplementation on Friction of Articular Cartilage
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5. Co-supervisor
Ing. David Nečas, Ph.D. / david.necas@vut.cz
6. Stays at other institutions (min. 7 days)
05/2018 – 07/2018 Contipro a.s., Dolní Dobrouč 401, 561 02 Dolní Dobrouč, Czech Republic
7. Teaching activities
Machine Design – Machine Elements (5KS) Machine Design – Mechanical Drives (6KT) Tribology (ZTR)
8. List of main publications
Papers in journals with IF:
TOROPITSYN, E., M. PRAVDA, D. REBENDA , I. ŠČIGALKOVÁ, M. VRBKA and V. VELEBNÝ. A Composite device for viscosupplementation treatment resistant to degradation by ROS and hyaluronidase. <i>Biomacromolecules</i> , 2021. (Under review)
ČÍPEK, P., M. VRBKA, D. REBENDA , D. NEČAS and I. KŘUPKA. Biotribology of Synovial Cartilage: Role of Albumin in Lubricant Film Formating. <i>Engineering Science and Technology, an International Journal</i> , 2021. (Under review)
REBENDA, David , Martin VRBKA, David NEČAS, Evgeniy TOROPITSYN, Seido YARIMITSU, Pavel ČÍPEK, Martin PRAVDA and Martin HARTL. Rheological and frictional analysis of viscosupplements towards improved lubrication of human joints. <i>Tribology International</i> . 2021, 160. ISSN 0301679X.

REBENDA, David, Martin VRBKA, Pavel ČÍPEK, Evgeniy TOROPITSYN, David NEČAS, Martin PRAVDA and Martin HARTL. On the Dependence of Rheology of Hyaluronic Acid Solutions and Frictional Behavior of Articular Cartilage. *Materials*. 2020, 13(11). ISSN 1996-1944.

LU, Xianjiu, David NEČAS, Qingen MENG, **David REBENDA**, Martin VRBKA, Martin HARTL and Zhongmin JIN. Towards the direct validation of computational lubrication modelling of hip replacements. *Tribology International*. 2020, 146(11). ISSN 0301679X.

ČÍPEK, Pavel, Martin VRBKA, **David REBENDA**, David NEČAS, Ivan KŘUPKA and Martin HARTL. Biotribology of Synovial Cartilage: A New Method for Visualization of Lubricating Film and Simultaneous Measurement of the Friction Coefficient. *Materials*. 2020, 13(9). ISSN 1996-1944.

FURMANN, Denis, David NEČAS, **David REBENDA**, Pavel ČÍPEK, Martin VRBKA, Ivan KŘUPKA and Martin HARTL. The Effect of Synovial Fluid Composition, Speed and Load on Frictional Behaviour of Articular Cartilage. *Materials*. 2020, 13(6). ISSN 1996-1944.

CHOUDHURY, Dipankar, **David REBENDA**, Shinya SASAKI, Pavel HEKRLE, Martin VRBKA and Min ZOU. Enhanced lubricant film formation through micro-dimpled hard-on-hard artificial hip joint: An in-situ observation of dimple shape effects. *Journal of the Mechanical Behavior of Biomedical Materials*. 2018, 2018-05-14, 81, 120-129. ISSN 17516161.

NEČAS, David, Martin VRBKA, **David REBENDA**, Jiří GALLO, Adéla GALANDÁKOVÁ, Lucie WOLFOVÁ, Ivan KŘUPKA and Martin HARTL. In situ observation of lubricant film formation in THR considering real conformity: The effect of model synovial fluid composition. *Tribology International*. 2018, 2018-05-14, 117, 206-216. ISSN 0301679X.

Papers in SCOPUS indexed journals:

RUFAQUA, Risha, Martin VRBKA, Dušan HEMZAL, Dipankar CHOUDHURY, **David REBENDA**, Ivan KŘUPKA and Martin HARTL. Raman analysis of chemisorbed tribofilm for metal-on-polyethylene hip joint prostheses. *Biosurface and Biotribology*. ISSN 2405-4518.

RUFAQUA, Risha, Martin VRBKA, Dušan HEMZAL, Dipankar CHOUDHURY, **David REBENDA**, Ivan KŘUPKA and Martin HARTL. Analysis of Chemisorbed Tribo-Film for Ceramic-on-Ceramic Hip Joint Prostheses by Raman Spectroscopy. *Journal of Functional Biomaterials*. 2021, 12(2). ISSN 2079-4983.

ČÍPEK, Pavel, **David REBENDA**, David NEČAS, Martin VRBKA, Ivan KŘUPKA and Martin HARTL. Visualization of Lubrication Film in Model of Synovial Joint. *Tribology in Industry*. 2019, 41(3), 387-393. ISSN 03548996.

9. Assessment of the supervision process

Very good

The supervision process followed the pre-set rules for PhD study. The process was based on one-month main meetings and on-demand discussions with supervisor, co-supervisor and colleagues from Biotribology Research Group. The candidate was always well prepared to discuss the issue of the dissertation including reflection of critical comments. The final PhD thesis and research papers were prepared in time and in sufficient quality. The outputs of PhD thesis have been three research papers. The teaching activities of candidate were focused especially on tutorials of courses of Machine Design – Machine Elements, Machine Design – Mechanical Drives and Tribology. The candidate attended three international conferences where he presented partial results of his research: Engineering Mechanics in

Svratka in Czech Republic, 16th International Conference on Tribology - Serbiatrib in Kragujevac in Serbia and 60th International Conference of Machine Design Departments in Hnanice in Czech Republic. He also contributed with his results to the presentation at the international conference (STLE Annual Meeting and Exhibition in the USA), without his personal participation.

10. Assessment of the candidate's ability to work independently

Very good

The candidate worked independently, based on the discussion with me and my colleagues from the lab and other experts from the field of biotribology, chemistry and orthopaedics. I would like to highlight the cooperation with Contipro company, where candidate completed a three-month internship and carried out rheological measurements of individual synovial solutions and commercial viscosupplements. The candidate independently designed a methodology of experiments based on the state of the art, performed experiments, and, according to the results analyses, he formulated conclusions. All of the publications, where he is listed as the main author, were prepared by himself. The candidate also supervised three bachelor theses and significantly participated in the other research projects of our Biotribological Research Group.

11. Assessment of the contribution that the research makes to knowledge in the field

Very good

The PhD thesis is composed from three papers in the journals with impact factor. Two of them were published in the journal "Materials", and last one was published in the journal "Tribology International". However, the candidate has also co-authored other biotribological publications, namely four publications in journals with impact factor and three in journals in Scopus database. The main scientific output of this thesis is the understanding of tribological and rheological behaviour of the model synovial joint, immediately after hyaluronic acid injection (that is, after viscosupplementation). The combination of tribology and rheology of viscosupplements is an understudied problem and this work helps to find answers to some of the questions. I believe that the obtained scientific findings will suite the future development of viscosupplements for better treatment of osteoarthritis. The main weaknesses of the PhD thesis are the lack of a deeper analysis of the results and what it means for actual cartilage lubrication (what lubrication regimes are present), what it means for cartilage wear (only friction and rheology were discussed) and what it means in terms of clinical outcomes and how we can improve viscosupplementation. I also find the thesis lacking a better correlation of the results between two presented models of synovial joint - cartilage against glass and PVA hydrogel against glass.

12. Other comments

none

13. Conclusion

PhD thesis is an independent scientific work that presents a novel solution to a significant problem in the research area and demonstrates the candidate's ability to conduct independent research.

YES



16. Date and signature	
27/07/2021	

Please note

- A. Evaluate categories 9 to 11 using the following scale: unacceptable, acceptable, satisfactory, good, very good, excellent.
- B. In each category 9 to 11 explain reasons for evaluation using between 100–200 words.
- C. E-mail the completed form to: Klara.Javorceková@vut.cz