| PhD study plan | | | | | | | |
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| PhD student | | | | | | Søren Havelund Welling | |
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| Date of birth | | | | | | 23rd of May 1986 | |
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| X | This is a revised study plan. | | | | | | |
|  | \* A letter with a description of all changes must be enclosed as a cover page to the study plan | | | | | | |
| On | | 23/05/2015 | | | this study plan is accepted by the following: | | |
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| PhD student’s signature | | | | | |  | |
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| Supervisor’s signature | | | | | |  | |
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| Head of PhD school/ Department’s signature | | | | | |  | |
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| Is the PhD student employed at DTU? | | | | | | | |
|  | Yes | | X | No | | | |
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| PhD committee | | | | | | |  |
|  | Chemistry, Biotechnology and Chemical Engineering | | | | | | |
|  |  | | | | | |  |
|  | Construction, Production, Civil engineering and Transport | | | | | | |
|  |  | | | | | | |
|  | Electronics, Communication and Space Science | | | | | | |
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|  | Life Science | | | | | | |
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| X | Mathematics, Physics and Informatics | | | | | | |
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| PhD school/ Department | | | | | | DTU Compute | |
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| Title of the PhD project | | | | | | Characterization of absorption enhancers for orally administered therapeutic peptides in “**Tablet formulations – applying statistical learning.** “ | |
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| Date of commencement | | | | | | 1st of May 2013 | |
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| Date of completion | | | | | | 30th of July 2016 | |
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| Supervisor | | | | | | Prof. Per Brockhoff, 45253365 | |
| \* Title, name, department | | | | | |  | |
| Co-supervisor | | | | | | Line Katrine Harder Clemmensen, 45253764 | |
| \* Title, name, department/company | | | | | |  | |
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| Project description (addendum) | | | | | | | |
| **Project description:** The focus of the project is towards the understanding of the structural properties important for oral absorption enhancement of therapeutic peptides and the mechanisms underlying their effects, together with essential properties pertinent for tablet formulation – overall a part in the technology of administering protein based pharmaceuticals orally.  **Statistical and machine learning tools** will be applied and developed to extract and comprehend more information from published data both scientific publications and patents –encompassing absorption enhancers. **Per Brockhoff** and **Line Harder Clemmensen** will supervise these aspects at DTU compute and **Hanne Refgaard** at Novo Nordisk.  ***The first part of the project*** (~1½ years) is focused on statistical learning. Literature data will be the basis for statistical classification models on absorption enhancement (recently collected), solubility and CMC to explore structure–activity/formulation relationships for absorption enhancers. The planned activities for the PhD student in this part are:  Collection of data from scientific literature and patents applying text mining/analysis tools  Calculate structural descriptors e.g. physicochemical properties for the collected compounds  Investigate, adapt and explore well-known statistical learning techniques to identify the most promising ones for the specific uses.  ***In vitro* cell culture-based models** (e.g., Caco-2) have been shown to be a valuable tool for assessing drug permeability and illustrating the absorption mechanisms of different permeation enhancers. This part of the validation the PhD student will perform under the supervision of **Stephen Buckley** at Novo Nordisk.  **The second part of the project** (~1 year) is focused on validation of the models developed in the first part of the project. A validation set of 10-15 compounds will be selected and the compounds will be tested in vitro for absorption enhancement in Caco-2 cells. Tablets with each compound will be produced, characterised and tested in rats. The planned activities in this part are:  1) Selection of validation set.  2) Testing of the compounds in vitro with focus on enhancement mechanism  3) Formulation of the compounds in tablets and in vitro characterisation of the tablets  4) Testing the compounds in tablets dosed orally to rat.  **Tablets produced** in the project will be made such that a platform is used enabling us to address the properties of the absorption enhancers in the characterization of the tablet This part of the validation will be performed by the PhD student under the supervision of **Lars Hovgaard** at Novo Nordisk.  **The *in vivo* performance** of the enhancers will be evaluated in rats and all ethic issues concerning animal testing will be addressed according to the Novo Nordisk guidelines for use of test animals.  **Addendum to second part of project:** To understand and communicate QSAR models, the tool-box models non-linear such as random forest, was found inadequate in the process of writing the article first article on *in vitro* cell culture based models. To solve this problem, a new promising technique was discovered, and time was allocated to pursue this method. The activities of this endeavour were:  1) Investigate the geometry of the random forest model in relation to the structures of data.  2) Implement and publish new methods as R-package. Optimize algorithms to reduce computation times.  3) Publish article on theory and usage of new found methodology  Due to extra activities, focus on physical tablet formulation and *in-vivo* are reduced. | | | | | | | |
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| External Research stay  (DTU strongly recommends that the external research stay takes place abroad) | | | | | | | |
| An external research stay will also be included during this part of the project and the intention is to visit Daniela M. Witten at in the Department of Biostatistics, University of Washington, US.  The timespan of the research stay is two months in the autumn of 2014 [Aug-Dec 2014].  **Addendum to external stay:**  Daniela M. Witten was finally unable to supervise in this period. Instead, a new external stay was chosen at the research group of Dr. Ing. Rodrigo Salas, Director of Department Ingeniería Civil Biomédica at the Facultad de Ingeniería, Universidad de Valparaíso, Chile. The content of the stay was to explore within fMRI models, the general curvature of random forest models when used to identify parcels of the brain associated with a given stimuli. This project was in part very different from pharmaceutical formulations, yet alike as a central part of my PhD have come to investigate the mapping curvatures of random forest models to understand how and what machine learning can captivate. There was a mutual understanding with Novo Nordisk that the external stay should not directly relate to drug development to avoid third-party conflicts of IP-rights.  The external stay took place from 1st of October 2014 until 18th of December 2014, thus nearly three months. | | | | | | | |
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| Educational requirements | | | | | | | | | |
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| \* For DTU courses: Specify course number, title, number of ECTS points and level (e.g. Master or PhD).  \* For non-DTU courses: Attach an *official* description including (The URL must be included if it is printed from a homepage): Course content and amount of ECTS points (1 ECTS equals 28 hours), workload in hours, method of examination and course provider. If the official description does not detail this information, an official statement should be obtained from the course provider (not assessed by the PhD student). The total number of ECTS points should be about 30, corresponding to approximately 840 working hours. | | | | | | | | | |
| \* For a definition of the various courses below, go to Course requirements on this [home page](http://www.dtu.dk/english/Education/phd/PhDguide/Study_plan). | | | | | | | | | |
| Courses at DTU with course numbers (*completed*)(~~discontinued~~)(replacement) | | | | | | | | | |
| ECTS no. |  | Couse no. |  | | PhD/Master’s | | |  | Course title |
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| *5* | *ECTS* | *27828* |  | | *PhD* | | |  | *Chemoinformatics in drug discovery* |
|  |  |  |  | |  | | |  |  |
| *7.5* | *ECTS* | *42790* |  | | *PhD* | | |  | *Business Course for Industrial PhD* |
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| *5* | *ECTS* | *02582* |  | | *PhD* | | |  | *Computational Data Analysis* |
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| ~~5~~ | ~~ECTS~~ | ~~02409~~ |  | | ~~Master~~ | | |  | ~~Multivariate Statistics~~ |
| ~~5~~ | ~~ECTS~~ | ~~41391~~ |  | | ~~PhD~~ | | |  | ~~High Performance Computing: FORTRAN, OpenMP and MPI (January 2015)~~ |
| *5* | *ECTS* | *-* |  | | *PhD* | | |  | *Special course in R package development* |
| External courses (A **print** of the official course description for each course *must* be enclosed – **attached** to the study plan **but not** pasted into the study plan) | | | | | | | | | |
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| ECTS no. |  | PhD/Master’s | | | |  | Course title | | |
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| *4* | *ECTS* | *PhD* | | | |  | *Analytical Methodology in Protein Formulation Development [B2]* | | |
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| 1.5 | ECTS | PhD | | | |  | EMTRAIN for European industrial PhDs in Pharmaceutical Research (April 2015) | | |
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| 2 | ECTS | PhD | | | |  | 2nd Data Storm Summer School (August 2015) | | |
| ~~3.5~~ | ~~ECTS~~ | ~~N/A~~ | | | |  | ~~Basic Pharmacokinetics, one week industrial summer school~~ | | |
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| Total number of ECTS points at PhD level | | | |  | | | | | |
| 30 | | | | | |
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| Total number of ECTS points at Master’s level | | | |  | | | | | |
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| \* Maximum 15 points at Master’s level. Bachelor courses can only be accepted in special cases and are subject to dispensation. | | | | | | | | | |
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| ECTS points in total | | | | 30 | | | | | |
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| Courses taken prior to the start of the PhD studies |
| \* Courses, which are part of another education, cannot be transferred. |
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| Dissemination requirements  (The expected dissemination activities for must be stated here. This applies to all PhD students.  Furthermore the compulsory workload for PhD students employed at DTU must be stated here) |
| \* Please state the time spent on each task in weeks and include each one in the time schedule below. The compulsory workload must not exceed six months, including the three months of dissemination requirements. If no compulsory work is listed, it means that the PhD student is free from any workload apart from the PhD project. |
| As Industrial PhD, no specific dissemination is strictly compulsory. Any dissemination was planned in consensus of PhD-student (SOWE) and supervisors. All dates are reconstructed and may be inaccurate by one week.  **Project presentations for 3 to 5 supervisors:**  NN ,29/8-13, (.7 week)  NN, 1/10-13 (.7 week)  DTU, 20/12-13, (.7 week)  DTU, 15/1-14, (.7 week)  NN, 2/9-14, (.7 week)  **Project presentations in departments and sections on DTU and NN:**  Project pres. at Section of Statistics and Data Analysis, DTU, 15/2/14, (.5 week)  Project pres. at Dept. Insulin Pharmacology,NN, 25/4-14, (1.0 week)  Project pres. for section vice president (JSTU), NN , 23/4-14, (.2 week)  Project pres. at Dept. of ADME, NN, 5/9-14, (1.0 week)  Project pres.,at Dept. of Oral Formulation Research, 22/-15 (.7 week)  Project pres.,at Section of Statistics and Data Analysis, DTU, (.7 Week), 19/2-15  Project pres. at Dept. Ingeniería Civil Biomédica, Valparaíso Chile, 15/10-14.(.5 week)  Project pres. at EMTRAIN workshop,Jansen Pharmaceuticals ,Antwerp, 27/4-14 (.2 week)  **Other presentations**  Internal NN project, Presentation on Citric Acid Mechanism, NN, 17/9-13,(.5 week)  Internal NN project, Presentation on Mechanisms of Absorption, NN, 5/8-14, (1.0 week)  Elevator pitch pres, DTU business course, 1/11-13 (.1 week)  Exam pres., 2 scientific censors, DTU business course, 26-11-13 (.5 week)  Data Ussing chambers, KU SUND, 5/1/14, (.1 week)  Multicore programming, rGroup, DTU, 3/4-14, (.5 week)  Winner of course poster competition, Data analysis course 02582, DTU, 05-05-14, (.7 week)  Mapping of non-linear methods in microarray, CBS, DTU 24/9-14, (.5 week)  **Conference talks:**  45 min. Talk, Visionday conference 2014, DTU, 14/5-14, (2.0 week)  20 minutes pres. at int. useR! conference, Aalborg 30/6-15 (1.5 week)  **Teaching (non-mandatory):**  1 day TA in random forest modelling, Dept Ingeniería Civil Biomédica, ~15/11-14 (.2 week).  TA in DTU course 27411, Compute DTU, 9/2-15 (.2 week)  5 hours guest lecturing course 27411, Compute DTU, 14/4-15 (.7 week)  5 hours guest lecturing course 02582, compute DTU, 5/5-15 (.7 week)  Co-supervising master thesis project with (LKHC), DTU, 01/02-15 ot 15/07-15 (2.5 week)  Supervisor for two master student interns from, École Centrale Lille, France, May-August 2015 (2.5 week)  **Writing articles**,  5 months |
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| Time Schedule |
| \* The time schedule should include courses, planned publications, dissemination activities, external research stay, time for detailed descriptions of subprojects, and for completing the PhD thesis (a short description per half year is strongly recommended). Complete the time schedule even if the later parts of the project are uncertain. It is expected to fill more than one page and may be included as an attachment. It may also be sent in as a Gantt table. |
| **June-July 2015**   * Submit 2nd article “Forest floor: Forest floor: a clear view on the topology of random   forests” to journal of information sciences.   * Present forestFloor package at useR! conference   **July-October 2015**   * Write 3rd article, “The curvature of QSAR: how molecular descriptors act in non-linear models to predict molecular solubility.” * 2nd Data Storm – 3 day summerschool   October-December, Test built models on NN  January: 3 week course  February-April: Write thesis  April 30th : hand in thesis |
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| Short description of the extent of the supervision |
| \* Please state the expected frequency of meetings etc. between PhD student and supervisor (Meetings must as a minimum be held every two weeks). Nature and frequency of other communication with supervisor should also be described in order to match the expectations of each part. |
| Meetings will take place individually with each of the five supervisors *ad hoc* when dealing with issues within their  scientific expertise. Beyond this Per Brockhoff together with Line Clemmensen are the University Supervisors, and  therefore a minimum meeting frequency every second week is employed during the periods of stays at the  university. Likewise Hanne Refsgaard is the main company supervisor, and a minimum meeting frequency every  second week will be employed. A meeting with the group of all supervisors are planned quarterly. A meeting is  either face-to-face, by telephone or skype. |
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| Career options |
| \* What are the career options? Both the private sector and the public sector should be considered. Please state thoughts about future work interests and consider whether these require special compentencies. |
| A research position in the big pharmaceutical industry, within protein formulation and drug  absorption in Denmark or abroad, Post Doc/contract or permanent position. Similar positions in academia.  A job within data analysis and/or statistical modelling have become increasingly interesting for me. |
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| Patents and innovations | | | |
| Is it expected that there are possibilities for developing any patentable technologies or software in connection with the PhD Project? | | | |
| X | Yes |  | No |
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| If yes: Be aware that the novelty of a patent is not damaged. Please contact the patent responsible at the department regarding disclosure and patent application. | | | |
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| Other matters | | | |
| \* Other matters of importance to the evaluation of the study plan may be stated here. | | | |
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| Abstract for the internet  (Please note! Only if your department needs an abstract of your project for its home page) |
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