Linking Process and Product models for Wet Granulation: A Compartmentalised PBM-CFD-DEM model framework for Fluidised Bed Spray Granulation

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Executive Summary

Computational models for wet granulation processes are increasingly being used to model industrial processes. We would like to be able to link process with product performance, however there is a mismatch between the outputs of process models (typically size, sometimes composition) and the inputs for product models (often agglomerate shape and structure, e.g. porosity and pore size distribution). We aim to bridge this gap, by building a wet granulation model framework which outputs agglomerate structure, in addition to size and composition (see Figure 1). In this project, we will:

1. Develop a hybrid model framework for wet granulation which outputs information important for product models.
2. Validate this model experimentally.
3. Provide explicit guidance for future model builders, through the publication of a review paper on linking process and product models for wet granulation.
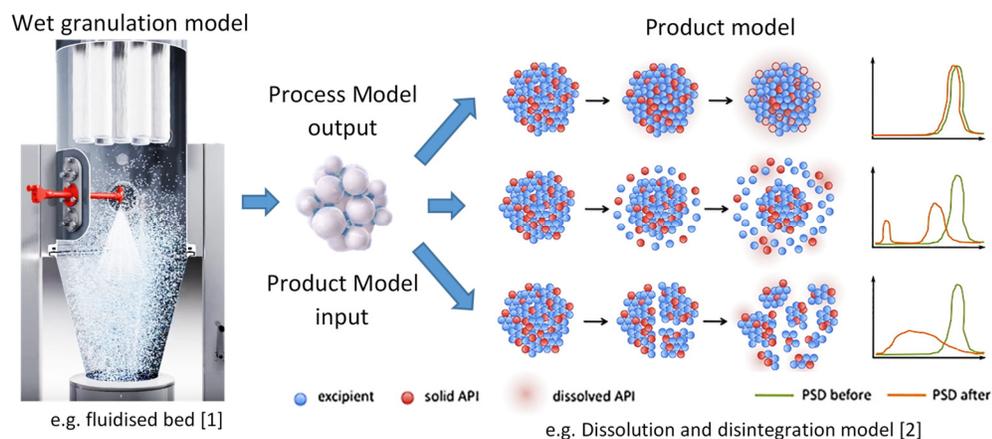

Figure 1: Schematic showing the linking of Process and Product Models

Introduction and Background

Wet granulation is a process used across a large range of industries. In particular, it is an integral operation in the pharmaceutical, food, minerals processing, consumer products and agrichemical industries. Over the past decades, huge strides have been made towards greater understanding of granulation processes, building micro-level understanding [3], regime maps [4, 5], process models [6-9], and product models [10-14].

Within a wet granulation process, particle and fluid interactions are occurring in multiple phases, and across multiple length scales. We have mechanistic models of many of these interactions, and there is great opportunity to apply these mechanistic models alongside modern computational techniques, to aid the design of granulation processes.

In granulation modelling, by far the most common dimension or parameter to be tracked is agglomerate size. However, agglomerate size is not the only input for product performance models. Many other parameters are important for these models, including agglomerate porosity and pore size distribution, wetting characteristics, morphology, and component content and distribution. To successfully link process models with product performance models, it is essential that the process model predicts the essential parameters for these performance models. In the future the linking of these process and product models, likely combined with the use of inverse methods, will enable genuine product driven process design and scale-up.

Modelling approach options

There are several key modelling approaches available to help predict granulation. Each have strengths and weaknesses, and critically, each have some very significant limitations. In this section, a brief overview is given of 3 common techniques: Population Balance Models (PBM), Computational Fluid Dynamics (CFD), and Discrete Element Modelling (DEM).

PBM: Population Balance Models are an excellent tool for process level modelling of granulation. The use of compartmentalised PBM has further enhanced the applicability of this method. However, PBM is restricted by the kernels used within it (often at least partially empirical), by the complicated solution methods required for multi-dimensional models, and by the limitations of the dimensions (or properties) which can be modelled. These limitations have

constrained the applicability of PBM for some industrial problems, and using these tools for reliable design and scale-up remains a huge challenge.

CFD: The hydrodynamic behavior of particulate processes involving multiphase flows can be captured by using CFD processes. These include Eulerian-Eulerian (EE) methods (based on two fluid theory) or Eulerian-Lagrangian (EL) approaches. In EE both particle-phase and carrier-phase are considered as a continuum, and their flow field is represented in an Eulerian reference frame. In contrast, EL approaches include a number of models in which the particle phase is considered as a discretely dispersed phase referenced in a Lagrangian frame, and the carrier phase is represented to be a continuum and its flow field is formulated in Eulerian frame.

DEM: Discrete Element Modelling (DEM) is an explicit numerical method that models the interactions of all particles in a domain. The particles are rigid but are subject to local deformation in places of contact and the resulting forces from particle overlaps are calculated. The motion of the particles is modelled on a particle-by-particle basis, which makes the method computationally intensive, and traditionally this has a large impact on the number of particles that can be feasibly simulated. However, advances in computational capacity have made DEM simulations in the order of hundreds of thousands to several millions of particles commonplace. DEM has been used extensively, both on its own and coupled with CFD. Particle positions are known with time, and when coupled with CFD, the particle motion can be influenced by fluid flow.

Comparison of Techniques: It is clear that each of these methods has a series of benefits, drawbacks, and limitations, some of which are summarised in Table 1. These limitations have been identified by several researchers [15-17], who have coupled various models together to enhance the model output, while minimising numerical complexity and computational resource. Many of these models have been successfully used to describe wet granulation, however they lack the modelling of the key particle structure information required to feed into product performance models.

Table 1 – Strengths and Limitations of Particulate Computation Modelling Techniques

Technique	Strengths	Weaknesses/Limitations
PBM	1. Computationally inexpensive 2. Compartmentally divides the particles into classes – distributed parameters 3. Ability to use mechanistically based rate process kernels	1. Kernels are often mainly empirically 2. Many parameters need to be estimated, some without physical explanation 3. Unable to provide particle dynamics
DEM	1. Tracks particle dynamics based on physical models 2. Important particle dynamics information such as collision frequency 3. Captures the effect of geometry and its influence on particles	1. Computationally expensive 2. Complex criteria required to define particle evolution 3. Difficult to measure parameters required for the contact model, and to calibrate 4. Difficult to apply to full industrial systems
CFD	1. Detailed insight into flow behavior of multiphase systems 2. Computationally efficient in comparison to DEM 3. User friendly for industrial applications	1. Unable to provide collision frequencies and collision forces in a particulate flow 2. Unable to provide changes to particle size and structure in a particulate flow

Aims and Objectives

The aim of this research project is to create an industrially applicable modelling framework for a wet granulation process, and to use this framework to model a fluidised bed spray granulation (FBG) process as a case study. The model will produce the outputs required for product performance models, with a particular focus on agglomerate structure (e.g. pore size, distribution of components). This will be achieved by meeting the following objectives:

1. Development of a 3-way coupled PBM-CFD-DEM for a fluidised bed spray granulation process
2. Development and implementation of a strategy for minimising the required data sets for experimental parameter estimation and model validation.
3. Completion of a comprehensive validation strategy. This will involve the separate validation of individual PBM compartments, the DEM model and CFD, to increase confidence in the model.
4. A proposal submitted to the EPSRC for complementary project funding, to leverage this work, and increase project positive outcomes.

Research Approach

Fluidised bed wet granulation has been chosen as the model system for this project. With current techniques and computing power, it is an almost impossible task to implement a model where "everything" is known and spatially and temporally resolved, and which is able to be solved *a priori*. However, it is achievable to produce a hybrid model which uses mechanistic models for the various rate processes which occur in the bed, and which outputs essential information for product models.

While the product models can vary widely, depending on the intended product use, across the board agglomerate structure is an essential component to product performance. There is evidence that the structure of agglomerates affect strength [14, 18], tabletability/compactability [12, 13], and dissolution and disintegration [10, 19]. Most models which successfully link with product performance models must include some information on agglomerate structure. For example, the recent agglomerate breakage model developed by Dosta and co-workers [14] presented DEM models for agglomerate breakage, and demonstrated that granule strength was highly dependent on the intra-granule distribution of components. There is potential for the results from this model (i.e. DEM generated structures) to feed directly into product models like this one.

A model fitting this description requires the thoughtful development of a model framework. **In this project, I propose we exploit each of the models for what they are good at, and avoid pushing them beyond their limits of usefulness.**

The first step in defining the modelling framework is to examine the granulator specifications and geometry, the probable rate processes occurring in the granulation, and the required outputs from the model. In the case of lab scale and manufacturing scale fluidised bed processes, granulators vary in dimension considerably. However, even lab scale fluidised bed granulators generally contain numbers of particles which are several orders of magnitude larger than can be comfortably modelled in a coupled CFD/DEM process.

FBG has complex and competing rate processes, which are difficult to model. However, fluidised bed granulators can be conceptually split into different geometric zones, in which different physical processes are occurring. This situation is ideal for compartmentalised PBM, as the geometric space can be separated into linked, simultaneously solved population balances, each containing only the required kernels to describe the dominant physical and chemical processes which are occurring in that volume, and has been demonstrated as a successful technique in the literature (e.g. [20-23]).

Figure 2 shows a conceptual model for a FBG process. It is proposed to split the fluidised bed into 2 PBM compartments: a spraying and layering compartment, and a bed compartment. The relevant rate processes are also summarised in the diagram. Selection and development of new mechanistic kernels for FBG is already occurring at The University of Sheffield as part of a current project, and this proposed project will build upon this work.
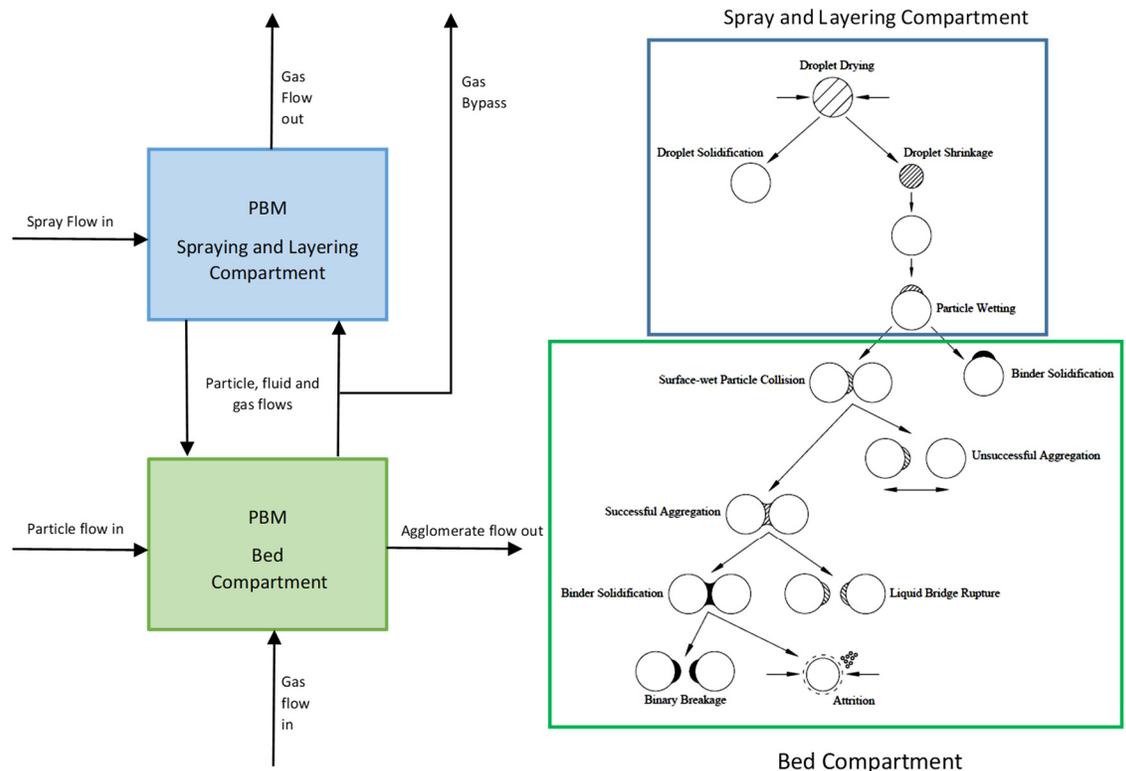

Figure 2: Proposed PBM Compartment Framework, and accompanying key mechanisms

A mechanistically based population balance with potential to be adapted for use in this PBM has recently been developed at the University of Sheffield. As an example of the mechanistic approach, an agglomeration kernel has been written which employs the particle coating number Φ_p [24] and Stokes criterion [3]. Figure 3 gives a conceptual view of the possible outcomes from different particle interaction scenarios. This kernel uses the particle coating number (Eq. 1) to calculate the fraction coating of the particle, F, with liquid (Eq. 2). Agglomeration success is then determined by the likelihood of liquid at the interface, and the Stokes criterion. If the viscous Stokes number St_v (Eq. 3) is smaller than the critical Stokes number St_v^* (Eq. 4), agglomeration will be successful. However, if St_v is larger than St_v^*, agglomeration will not be successful.

$$\Phi_p = \frac{6\, X_{LS} a_d}{\pi\, d_d^3 \rho_d A_{SA}}$$
Eq.1 [24]

where Φ_p is the particle coating number, X_{LS} is the liquid-solid mass fraction, a_d is the footprint area of a single droplet, d_d is the volume equivalent spherical diameter of the droplet, ρ_d is the liquid density and A_{SA} is the specific surface area of the particle.

$$F = 1 - \exp(-\Phi_p)$$
Eq. 2 [24]

$$St_v = \frac{8\, \rho d_p U_o}{18\mu}$$
Eq. 3 [3]

where ρ is the granule density, d_p is the surface average particle diameter, U_o is the initial relative granule collisional velocity and μ is the liquid viscosity.

$$St_v^* = \left(1 + \frac{1}{e}\right) \ln\left(\frac{h}{h_a}\right)$$
Eq.4 [3]

where e is the coefficient of restitution, h is the thickness of the liquid surface layer and h_a is the characteristic height of surface asperities.

Figure 3: Potential Outcomes from Particle Collisions

Compartmentalised population balance models require key inputs which can be difficult to provide. In addition to a large list of material properties, many of which can be measured, calculated or approximated, there is key information about particle flows, occupancy, and velocities which are difficult to predict. To provide some of this information, we propose to link the compartmentalised PBM to a Eulerian-Lagrangian model for FBG, using Multiphase Particle-in-Cell (MP-PIC) [25]. This method has been shown to be accurate and reliable in simulating flows in fluidised beds, and is significantly faster to solve than CFD-DEM simulations.

This MP-PIC model will provide key information on the size of the fluidised bed compartments, and also provide mass flows into each of the compartments. It is expected that ANSYS Fluent will be used.

Small "Unit Cell" DEM/CFD models will be developed to provide agglomerate structure. As discussed earlier, DEM/CFD is extremely expensive to run. However work at Sheffield is ongoing into the use of these Unit Cell simulations, which are used to simulate very small volumes of a process unit ([26, 27]). By using DEM/CFD, intra-granule particle arrangements can be modelled, and these structures can be analysed to provide information such as void size distribution, overall porosity, and intra- and inter- granule distribution of components. Alternatively, the structures generated using DEM could be inputted directly into product models (e.g. [12-14]). There is also excellent potential to use this technique to input information into the PBM (e.g. collision frequencies and forces). It is expected that the DEM/CFD Unit Cell simulations will be modelled using EDEM and ANSYS Fluent.

The design of these small scale DEM/CFD simulations requires careful thought, and many options remain for the coupling of the models. Coming to these decisions will form part of the initial model design phase. A high-level schematic of the proposed modelling strategy is shown in Figure 4.

Model validation is always an essential and challenging element of model development, and in the case of combined
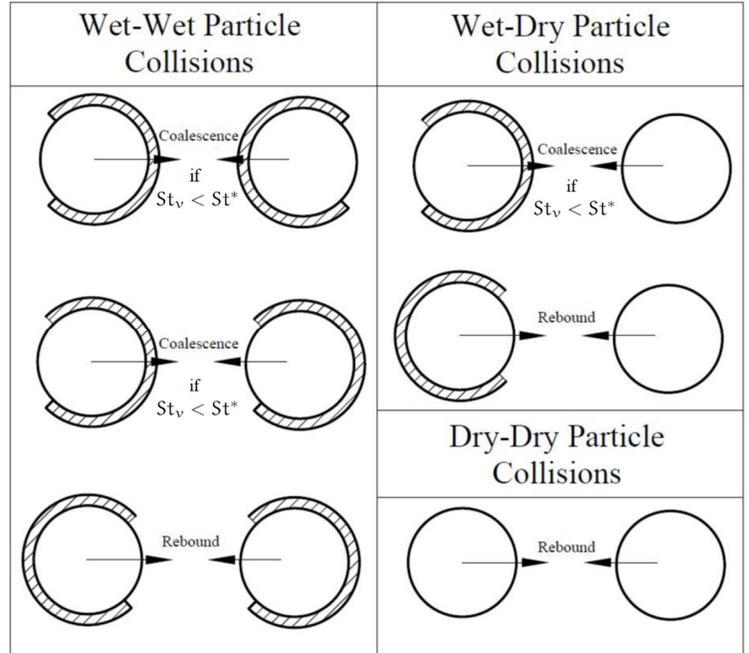
models such as this, robust and careful validation becomes even more difficult and important. A clear model validation strategy will be developed as part of this project. Many options for experimental validation exist. We expect to develop small scale "smart" experiments to individually test the two PBM compartment models, the DEM/CFD simulations, and the MP-PIC CFD simulations, in addition to running lab scale fluidised bed experiments. Available agglomerate characterization techniques include particle size measurement (laser diffraction, sieving), optical microscopy, image analysis techniques, SEM with EDS, and micro CT (voxel size ~1 µm). We also have PIV available, to characterise fluidised bed flow and validate MP-PIC. Particular attention must be paid to validating particle structure outputs.
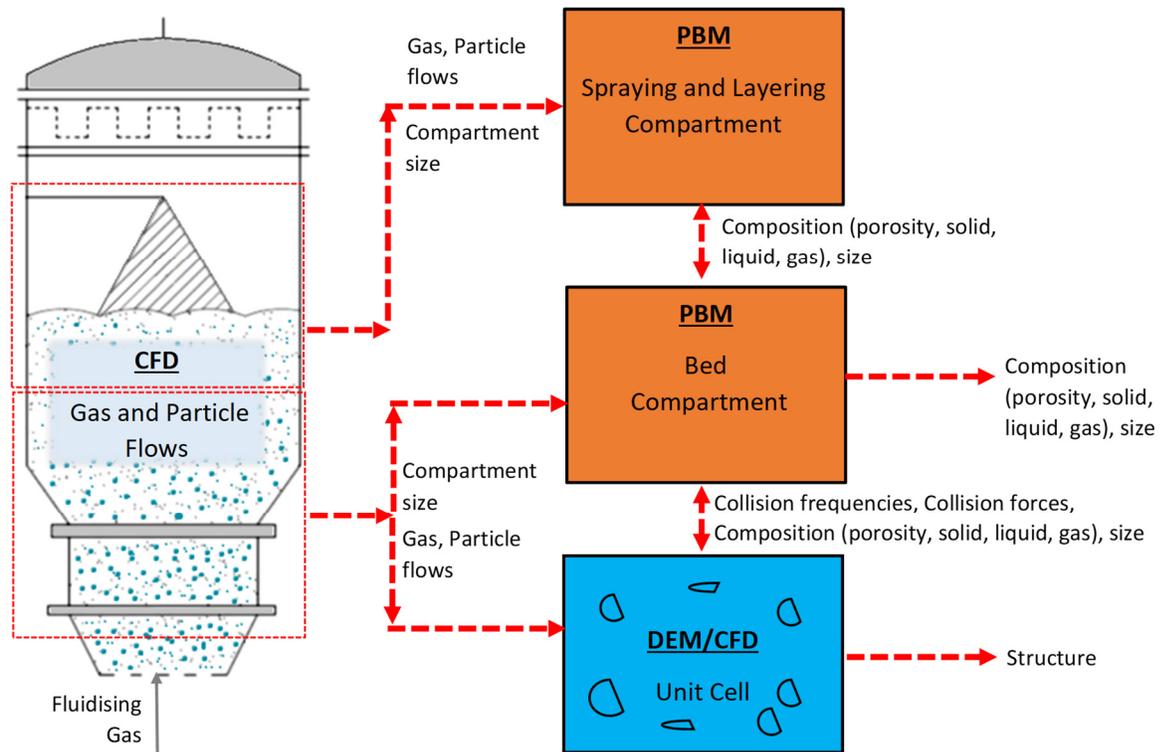
Figure 4: Preliminary high-level model coupling structure

Workplan, Deliverables and Milestones

This is an extremely challenging problem, which requires an integrated modelling approach. This project can be split into a series of individual tasks, as described below:

Tasks:
T1 – Literature review. A comprehensive literature review will be conducted, and will form the basis for the review paper (see milestone M1)
T2 – Overall model structure and coupling development
T3 – Population Balance Development – Spray and Layering Compartment
T4 – Population Balance Development – Bed Compartment
T5 – Fluidised Bed CFD Simulations
T6 – Fluidised Bed Flow Validation
T7 – Experimental Validation - Spray and Layering Compartment
T8 – Unit Cell DEM Development – Bed Compartment
T9 – Experimental Validation - Bed Compartment
T10 – Hybrid PBM-DEM-CFD Simulations
T11 – Hybrid PBM-DEM-CFD Experimental Validation
T12 – Model modification and testing of predictive capability

Milestones:
M1: Submission of a grant proposal for complementary funding from the EPSRC (Manufacturing the Future Theme, Responsive Mode).
M2: Submission of Computational Modelling in Wet Granulation Review Paper. This paper will contain a comprehensive review of the available computation tools for wet granulation, and will provide guidance on model development, with an emphasis on developing links between process and product models.
M3: Annual Report 1
M4: Annual Report 2
M5: Final Report 3

Leverage Existing Programmes and Facilities

There are several current and former projects within the Particle Technology Group which will be useful in this project. In particular, we have an ongoing project on PBM of fluidised bed granulation, which will significantly aid this work. We also have a project on the coupling of PBM (gPROMS) with DEM (EDEM) for a twin screw granulator. Additionally, we are currently conducting Unit Cell DEM simulations of granule breakage in particle flows, and this experience directly applicable to the Unit Cell DEM simulations proposed here.

We have a broad range of experimental and state of the art characterisation equipment, including 3 fluidised beds of varying scales. Of particular importance is the recent purchase of an Oxford Laser VisiSizer N60V System, which is able to measure drop size and drop velocities for liquid sprays.

This is an ambitious project. To support the project and improve the outcomes, I propose to leverage some current postdocs' expertise for this project. Dr. Omid Tash is currently working on PBM, and has significant experience experience in CFD. Omid will overee the MP-PIC development, and integration with PBM. Dr Li Ge Wang is a DEM expert, and is working on the PBM/DEM model for twin screw granulators, in addition to the current Unit Cell development. Li Ge will provide advice on the new Unit Cell DEM development, and on the interface with PBM.

While this project is achievable within the financial constraints, it could benefit from additional, complementary project funding. A key milestone for this project is the submission of a proposal for EPSRC funding, focused on the development of process models which are able to link with product models.

Opportunities for Collaboration with IFPRI Partners

There is excellent potential to work with IFPRI partners on this project. I have had discussions with Nestle and Roche in particular, and there are very good opportunities to work with these companies, and other IFPRI partners. Potential avenues include supplying materials of interest, potentially hosting the PhD student to conduct experimental validation experiments, or opportunities to work with the industrial modelling teams.

Our research group already has active research collaboration with several IFPRI partners (e.g. Roche, Syngenta, Lilly, Roche, P&G, PSE), working on projects ranging from studentships to the large consortium CMAC Future Continuous Manufacturing Hub. This project creates excellent opportunities to strengthen these links, and develop new ones.

Resources

The project budget is $38k/yr for 3 years. This will be primarily used to fund a PhD Student at The University of Sheffield. Using a conservative exchange rate of GBP £0.73 per USD, PhD tuition fees amount to approximately $6200/year, and a typical PhD student stipend is $20600/year. This comes to a total of $26800/year. $2000 will be budgeted for travel to the annual IFPRI meetings. The remaining $9200 per year will be spent on laboratory consumables and software licenses.

To support this project, a fraction of Dr Omid Tash's time will be devoted to the project (funded from other sources), to help ensure the project success. In addition to my normal involvement, I am expecting to take a semester sabbatical in Autumn 2019, and I intend to make this project the focus of my sabbatical leave. This will provide an excellent opportunity to make an accelerated start to the research.

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Project Gantt Chart

Task	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
T1 – Literature review	■	■	■	■	■	■																														
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