Model Assisted Design of Granular Products Project Renewal
Development of a Framework for Model Assisted Process Design

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1. Introduction and Background

Wet granulation is an integral size enlargement operation in the pharmaceutical, food, minerals processing, consumer products and agrichemical industries. In some cases, granular products form the final product (e.g. agrichemicals, foods, and some consumer products). In others, granulation forms an essential intermediate process step in the manufacturing of tablets (e.g. pharmaceuticals and consumer products), with significant effects on downstream processing and tablet performance.

Within the community, the ability to design, predict and control granulation and other powder/particle manufacturing processes has improved substantially over the past decades. This has been due to dedicated research into the mechanisms and rate processes (e.g. [1-3]), and also significant efforts to improve and create new methods to computationally simulate these processes [4-10]. The ability to apply these computational methods to reduce the experimental burden in achieving desired particle attributes is now an area of active investigation [4, 11, 12].

The focus of these methods, however, remain on ***final particle attributes***, or critical quality attributes. These are typically properties of the final granular materials which are known to be important for the performance of the granular product, without actually demonstrating how these attributes ***influence the performance of a product***. These properties often take the form of a single number used to describe a population (e.g. d_{43}, bulk density) and are typically arbitrary or based on trial and error and engineer experience. Crucially, this presents very limited opportunity to optimize the process to achieve better performance or cheaper, more sustainable processes.

In contrast to process model research and development, product performance model development is under-studied, and research into the linking of process and product performance models is only just starting. This is clearly an important and exciting frontier for both industry and academic research, and this project represents an excellent opportunity to demonstrate and guide the use of linked process-product models for the design of granular products.

1.1 Summary of Current and Expected Phase One Outputs

The primary aim of the first phase of this research (2019 – 2023) is to investigate the ability to link process and product models for wet granulation, with additional research into inverse methods to effectively "reverse engineer" the problem, i.e. to predict the required process conditions to give desired product performance. This is shown schematically in Figure 1.

Process models for wet granulation have benefited from recent research focus and are relatively well developed, however complementary product performance models are not yet as mature. Due to this, a substantial proportion of the initial project has been dedicated to the development of a robust product performance model which is suitable for coupling with current process model outputs.

By the end of the first phase of this research project (Nov 2023), we expect the following broad research advances to be achieved:

1) A new product performance model describing granule disintegration and dispersion will have been developed (complete), methodology for verifying and parameterizing the model will be identified (complete) and the model will be verified experimentally (ongoing, expected 2023)
2) A population balance model for high shear granulation will be identified (complete), the key structural information for the process model outputs/product model inputs will be identified (complete) and the model will be verified experimentally (ongoing, expected 2023)
3) Methodology for solving the inverse problem will be identified (complete), and progress will be made towards the generation of surrogate models for inverse problem solving (ongoing, expected 2023)

Detailed results from the first phase of the project can be found in Annual IFPRI reports ARR-59-02, ARR-59-03 and ARR-59-04.

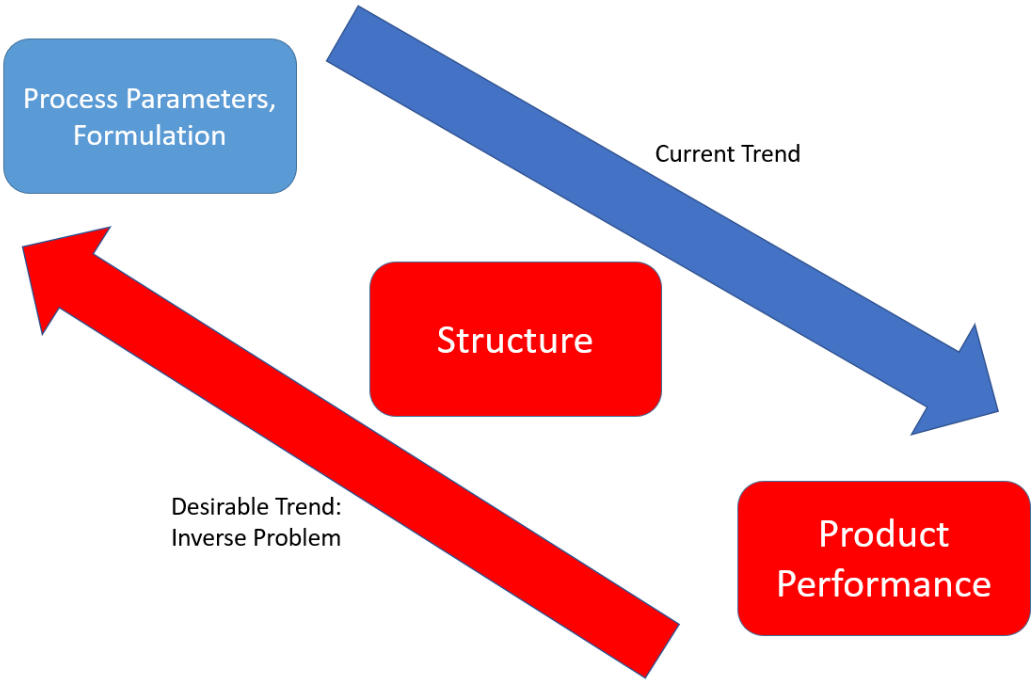

Figure 1: Linking a process model with a product performance model, with granular properties (structure) as the linking feature.

1.2 Renewal Aims and Objectives

It is clear that much work remains in the broad area of linking process and product models to assist in particulate process design. By the end of the first phase of this IFPRI project, we expect to demonstrate the potential of these linked models with a case study of a linked high shear granulator model with a swelling driven granule dispersion model. There are several clear opportunities to extend this research.

In the next phase of this project, we intend to expand the applicability and test the ability of this process-product linking approach to:

1) Include multiple process models by adding a fluidised bed spray granulation model [13] (available at Sheffield and implemented in gPROMS).
2) Include multiple product performance models by adding a new model for granule strength.
3) Apply the latest techniques to efficiently and effectively solve the inverse problem for this 2 x 2 scenario, including the development of surrogate models for each of the process and product models, and thorough global sensitivity analysis and confidence testing of the models.
4) Develop guidance for the use of modelling approaches such as these in industry to reduce lab, pilot and full scale plant trial burden, taking into account the confidence required in the models.

By achieving these aims, we will establish the ability to use linked process and product models to ***optimise granule performance*** across multiple desired performance characteristics, choose ***appropriate process conditions***, and also inform ***the choice of processing equipment*** itself. In the process we will also ***identify challenges and limitations*** in this approach, and critique model sensitivity and confidence in the outputs. Working with IFPRI members to provide further industrial insight, we will give a realistic picture of current applicability of this approach to industrial granulation.

2. Proposed Research Approach

By November 2023, it is expected that a high shear wet granulation model will be linked with a granule dispersion model for granules, and the process of developing surrogate models for each of these models will be underway, enabling solution of the inverse problem.

We propose to further extend this work to examine the ability to incorporate multiple process models (Work Package 1), multiple product models (Work Package 2), and to examine the challenges in solving these multi-process/multi-performance model optimization problems (Work Package 3). Finally, guidance for the implementation of model frameworks such as this in industry will be developed. Figure 2 gives a high level overview of the modelling approach.

It must be acknowledged that the objectives of this proposal are ambitious, and each of the work packages presented in this proposal represents substantial, novel, useful yet challenging contributions to the field. As has been the case in the initial project, risk will be mitigated by working closely with our IFPRI liaisons and the broader IFPRI team, and if necessary by narrowing the scope to achieve the broader aim of the project.

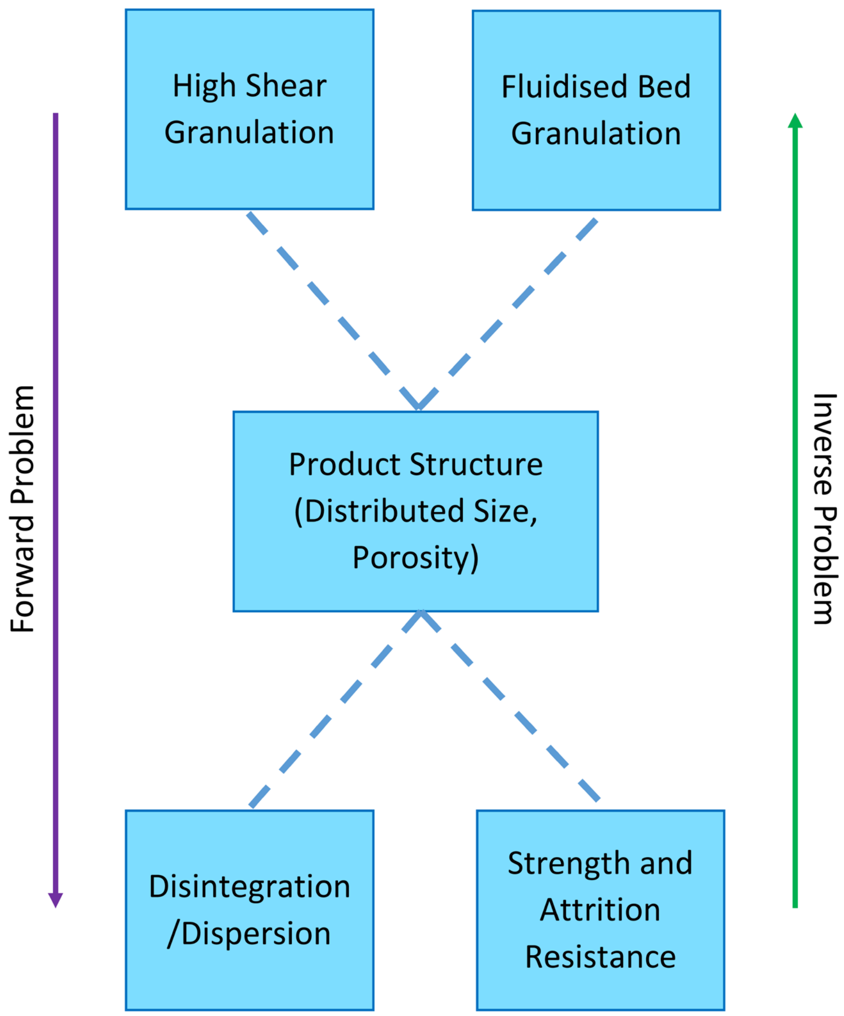

Figure 2: Proposed Expanded Process-Product Model Structure.

2.1 Project Work Package Descriptions and Timelines

Work Package 1: Implementation of multiple granulation process models (M1 – M18)
In this renewal project, emphasis will be placed first on incorporation of another existing process model to the framework. In particular, we will use an existing model developed at the University of Sheffield for fluidised bed spray granulation [13], which has been fully implemented in gPROMS FormulatedProducts. This model will be incorporated alongside the High Shear Wet Granulation Model used in Phase 1 of the project. WP1 will include model sensitivity analysis, verification and parameter estimation.

Work Package 2: Implementation of multiple granule performance models (M13 – M30)
The granule disintegration and dispersion model developed in Phase 1 of this research presents a single product performance model for process optimisation, however it is well known that there can be competition between different granule performance characteristics. For example, as porosity increases, granule strength typically decreases, while the effects of

porosity on granule dispersion are complicated due to multiple simultaneous rate processes, which are highly linked with material properties.

In this work package, a simple model for granule strength will be developed, which is suitable for coupling with process models from WP1. This will allow for the optimisation of granulation processes for two granule performance characteristics: dispersion kinetics and granule strength. Several models for granule strength exist in the literature, and the first approach will be to adapt and simplify existing strength models to suit the model framework. For this project, as stated in the original project brief, it is important that the distributed nature of granular products is represented, both in the granule properties and performance characteristics. Starting points for models have been identified (e.g. [14-16]), however these will require some work to be suitable for coupling with process models and minimizing computational resource requirements. Following development, the model will be verified and validated.

Work Package 3: Surrogate Model Development and Inverse Problem Solving Methods (M1 – M36)

Surrogate model and machine learning development is becoming increasingly sophisticated and applicable to particulate processes, especially when combined with mechanistic models. By combining these two methods, many advantages can be realised:

1) Mechanistic models are verified and validated using limited experimental data, and these models are then used to generate the large training sets required for machine learning and surrogate model development, thereby reducing experimental burden.
2) The surrogate models provide feedback on the mechanistic models, and in some instances can be used to reduce the complexity or improve rate expressions of mechanistic models based on the parameter sensitivity results
3) The generation of surrogate models in effect provides the means to determine sets/spaces of operating conditions to satisfy required product performance characteristics.

There are several methods which may be applied to this problem, including neural networks and polynomial chaos expansion (e.g. [17, 18]). Gaussian Processes [19-21] provide a particularly promising approach, and this method has already been applied to the high shear granulation population balance model used in this IFPRI project [22]. For WP3, we propose to continue working closely with Prof Solomon Brown and his research group at the University of Sheffield, who are experts in the field of machine learning and surrogate model development.

The key output of WP3 with be solution of the overall inverse problem, which will indicate choice of equipment type (high shear or fluidised bed granulation) and process conditions to produce granules with the desired dispersion kinetics and granule strength. Importantly this will also include robust analysis of the confidence in the results, and provide guidance on the currently ability to use linked process-product models for industrial process design.

2.2 Leveraging Existing Programmes and Facilities

Sheffield has an excellent working relationship with Siemens PSE, and our researchers continue to work regularly with PSE to develop and use gPROMS in our research. This relationship has developed further as part of the IFPRI project and other collaborative endeavors, and combined with the modelling expertise at Sheffield is an excellent contribution to the project.

In addition, our role as part of the CMAC EPSRC Pharmaceutical Manufacturing Hub is very beneficial to the proposed research. In this Hub, Rachel Smith leads the work on developing mechanistic models for tablet dissolution and disintegration, and this has clear areas of complementarity with this proposal.

In collaboration with Daniel Markl at the University of Strathclyde, we have been refining techniques for investigating granule swelling, breakup and dispersion using real time optical coherence tomography (OCT) and complementary image analysis. This forms part of the IFPRI Collaboration Grant "Model calibration as a Tool for Material Characterisation". We continue to collaborate closely, and share the excellent combined characterisation and granulation equipment between our groups.

2.3 Opportunities for Collaboration with IFPRI Partners

We have maintained strong connections with our IFPRI Liaisons throughout the project, and appreciate the steer and advice they provide on the project. We currently meet regularly with Poul Bach from Novozymes, Michael Brozio from Syngenta and Joris Salari from Corbion, and previously enjoyed working with Sri Sharath Kulkarni while DFE Pharma were members. This research project is highly industrially relevant and can benefit greatly from both industrial steer and real industrial data. We welcome further input, and believe expanding the project to include fluidised bed granulation and granule strength modeling will broaden the applicability even further.

2.4 Resources

The project budget is $40k/year for 3 years. This will be primarily used to fund a PhD Student at The University of Sheffield. Using current exchange rates, PhD tuition fees amount to approximately $6200/year, and a typical PhD student stipend is roughly $22000/year. This comes to a total of $28200/year. $2000 will be budgeted for travel to the annual IFPRI meetings. The remaining $9800 per year will be spent on laboratory consumables and software licenses.

3. References

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