Predictive Framework for Multicomponent Powder Compact Strength

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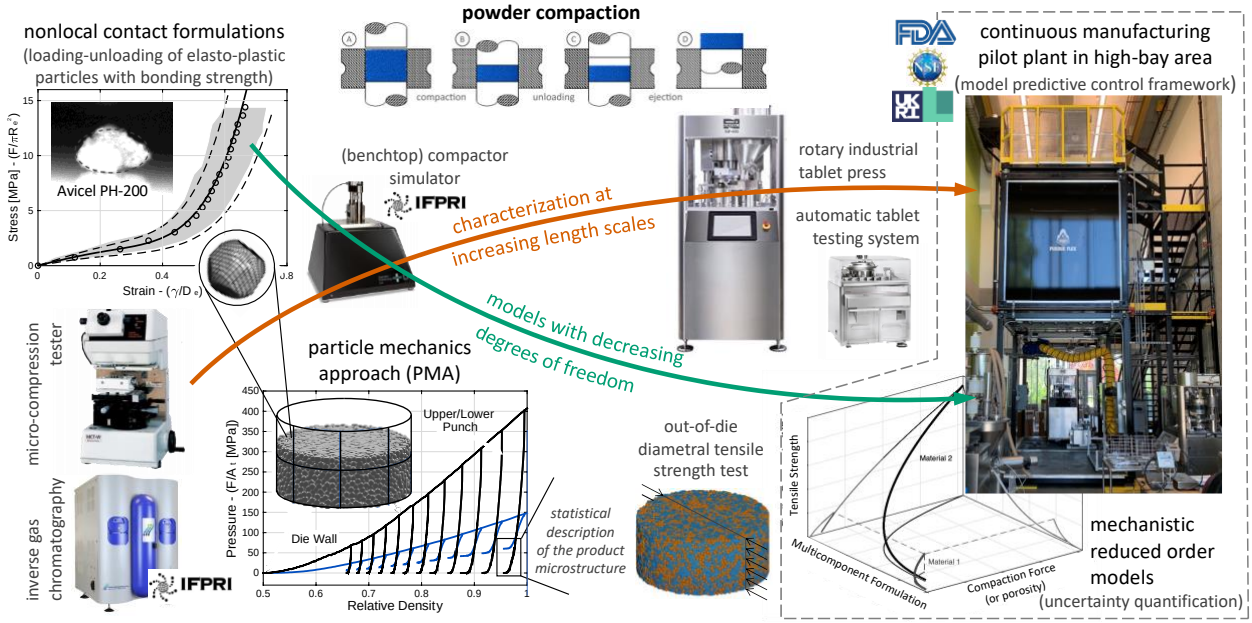
Scope

This effort addresses the request for proposals for a *predictive framework for strength development in multicomponent powder mixtures undergoing cold compaction at compaction stresses large enough to cause significant plastic deformation of particles* by the International Fine Particle Research Institute.

Objective

The objective of this proposal is to develop a particle-level predictive framework for estimating microstructure evolution and strength formation during cold compaction of multicomponent powder mixtures. Specifically, the framework will predict inter-particle and particle-wall forces, taking into account the large-scale elastic and plastic deformation of the particles during compaction, and the formation of inter-particle solid bridges during the creation of bonding area. Following the compaction portion of the model, the punch face will be retracted, and the particle bed response will be modeled, taking into account the elastic recovery of the plastically deformed particles and the fracture toughness of inter-particle solid bridges. The punch will be assumed non-adhesive. Lastly, the ejection of the compact from the die will be modeled, accounting for further elastic recovery and loss of strength.



Developing and applying the proposed solid mechanics-based modelling framework to multicomponent formulations entails several challenges including: (i) a realistic definition of the material's microstructure, (ii) the definition of inter-particle and particle-wall contact laws governing microscopic and interfacial phenomena, (iii) particle-level characterization techniques to estimate the mechano-chemical properties in these contact laws, and (iv) efficient computational algorithms capable of evolving the microstructure by following the interaction between all constituents. For highly dense granular systems under large deformations, the **particle mechanics approach** (PMA) [**Task 1**] is one of the most effective approaches for describing the behavior of all particles in the microstructure [2-5]. It employs **non-local contact formulations** (NLC) [**Task 2**], which remain predictive at large deformations by removing the restricting, nevertheless ubiquitous, assumption of independent contacts inherent in discrete analyses based on pair-interactions [1, 6-10]. Additionally, particle-level mechano-chemical

properties need to be calibrated from particle-scale experimental characterization using, for example, a **micro-compression tester** and **inverse gas chromatography** [Task 2]. The PMA describes each individual particle in the granular system, where the collective rearrangement, deformation, and bonding **strength formation** [Task 3] of the particles results in the macroscopic properties of the compact. The shape of the particles will be approximated to be spherical. Inter-particle friction and intra-particle breakage will not be considered. This multiscale modeling, simulation, and characterization framework (graphically conceptualized above) will be validated before being used to elucidate the relationship between particle-level properties and tensile strength of multicomponent powder mixtures [Task 4].

To achieve these research objectives, the PIs will leverage their extensive experience related to powder compaction and pharmaceutical manufacturing, as well the CP3 Characterization Lab and technical results obtained through past and on-going collaborations, including research efforts sponsored by the U.S. Food and Drug Administration (FDA): Risk-based Process Synthesis and Industry 4.0 Framework for Pharmaceutical Manufacturing Processes and by the U.S. National Science Foundation NSF: Engineering Research Center on Structured Organic Particulate System as well as CMMI-EPSRC: Right First Time Manufacture of Pharmaceuticals, and training efforts sponsored by the FDA and NIPTE (National Institute for Pharmaceutical Technology and Education): Continuous Pharmaceutical Manufacturing of Drug Products Hands on Training Course. The development of **reduced order models for product development and process control** from the outcome of Task 4 remains a topic of interest, though it is beyond the scope of this project.

Proposed Approach

Per the relevant RGO, the proposed effort encompasses three years of research and is expected to cost US$42,000 per year. The effort will consist of the following four research tasks:

Task 1: Statistical description of microstructure formation and evolution in compacted granular materials

The particle mechanics approach (PMA) for highly dense granular systems, developed by Gonzalez et al. [1,2], describes each individual particle in the powder bed, and the collective rearrangement and deformation of the particles that results in a quasi-statically compacted specimen. An equilibrium configuration is therefore defined by the solution of a system of nonlinear equations that corresponds to static equilibrium of the granular system, i.e., the sum of all contact forces acting on each particle equals zero. Hence, microstructure formation and evolution are not obtained by artificially damped or cooled-down dynamic processes, using dynamic discrete element methods, but rather by trust-region iterative solvers that follow the energy landscape around the solution of static equilibrium. The particle mechanics approach has been used to predict the microstructure evolution during die-compaction of elastic [2], plastic [5], and elasto-plastic [3,4,8] spherical particles up to relative densities close to one. By virtue of the computational efficiency of the approach, these large simulations have enough statistical significance to predict accurate distributions of microstructure descriptors (e.g., contact force magnitude and orientations [5], bonding interfaces [8], pore space morphology [12]).

Figure 1 shows a validation of the PMA predictions of inter-particle and particle-wall (i.e., particle-punch and particle-die wall) contact forces, using a NLC for elastic spheres [1]. The agreement is remarkable, revealing for the first time that the distributions of forces and contact interfaces in the bulk become progressively different from those at the compact surface [2]. Figure 2 shows PMA predictions for spheres with hardening plastic behavior utilizing *low fidelity* plastic contact laws (i.e., utilizing pair contact interactions, as opposed to NLC formulation). The results indicate that the evolution of the contact force network and the formation of bonding area (i.e., of contact interfaces) depend on the plastic hardening exponent [5]. Similarly, by endowing elasto-plastic contact laws with interparticle bonding strength, PMA simulations indicate that the creation of bonding area depends on mechano-chemical properties of the interacting particles (i.e., on elastic and plastic properties as well as the interfacial fracture energy of inter-particle solid bridges) [3,8,11].

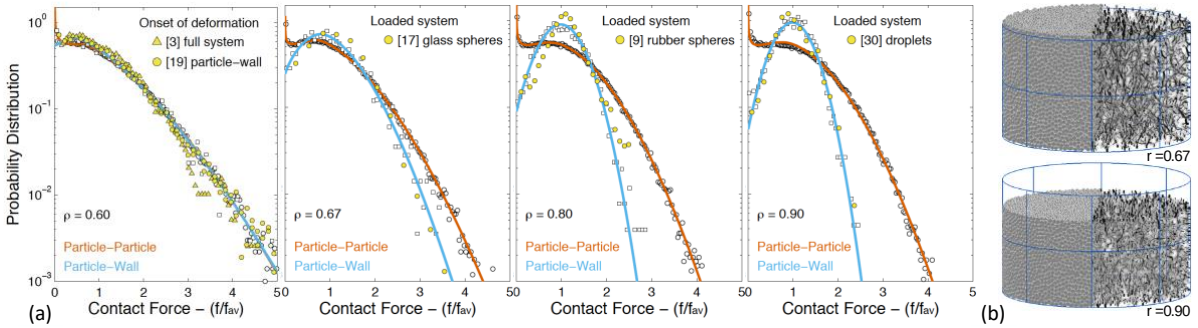


Figure 1. Probability distribution of inter-particle and particle-wall contact forces in a large monodisperse packing of elastic spherical particles. (a) Agreement between distributions experimentally obtained (symbols, see references in [2]) and predicted by the nonlocal contact law [1-2] at different relative densities. (b) Heterogeneous and anisotropic network of forces at two relative densities [2].

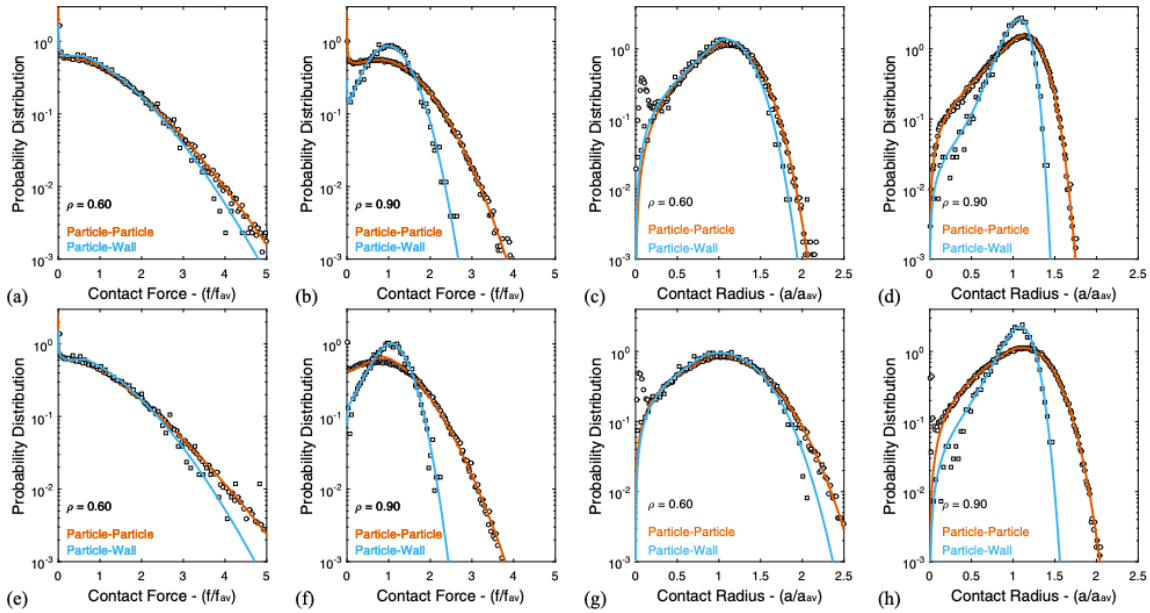


Figure 2. Probability distribution of particle-particle (circles) and particle-wall (squares) forces (left) and radii (right) determined from particle mechanics simulations of 40k packings of plastic spheres with hardening exponent equal to 1 (top) and equal to 5 (bottom).

Proposed work: This task will address the most industrially relevant, perhaps most challenging open problem in this research area, i.e., the elucidation of a particle-level, predictive and computationally efficient framework for estimating microstructure formation and evolution in compacted elasto-plastic particles with bonding strength using nonlocal contact formulations. Among other tasks, this will require the coupling of PMA with three-dimensional computations of Voronoi tessellations (e.g., with Voro++). *Evidence for plausibility*: This framework has been developed by Gonzalez et al. for elastic NLC formulations solving two sets of coupled nonlinear equations using a staggered numerical scheme that combines a trust-region iterative solver (for equilibrium equations) and a fixed-point iteration scheme (for nonlocal deformations). The efficacy of the approach has been validated experimentally, see Figure 1 and [2].

Risk identification: Particles are approximated to be spherical. *Mitigation plan*: Irregular particles with medium-to-high roundness and sphericity have moderate effects on the initial but not on the later stages of compaction, when bonding strength is formed [3,4,7]. Particles with low roundness and sphericity will be excluded from the testbeds considered in this project (see Task 4).

Risk identification: NLC elasto-plastic contact laws might not be amenable to general loading configurations, or they might be computationally costly. *Mitigation plan*: Low fidelity laws for elasto-plastic particles with bonding strength have been used to estimate tensile strength successfully [3,11]. Their adoption might be in detriment of a very accurate mapping between particle-level properties and compact strength.

Task 2: Concept of non-local contact formulations and mechano-chemical characterization of particles

Figure 3a shows that the utilization and, thus, development of NLC formulations is of paramount importance for attaining good predictions of the inter-particle force and bonding area. These formulations need to account for elasto-plastic loading [9], with strain hardening [10], and for elastic unloading with the formation of solid bridges [8]. Furthermore, they need to depend on the loading configuration [1, 6, 9-10] by accounting for non-local contributions using a (semi-)analytical formulation, for computational efficiency. The principle of superposition used to derive nonlocal deformations in elastic particles is not readily applicable to plastic particles. However, the well-established assumption of volume-preserving plastic deformation together with the stiff elastic compressibility available at high levels of confinement allow for developing solid mechanics-based nonlocal plastic contact laws which capture the physical mechanisms observed under different loading configurations [9-10].

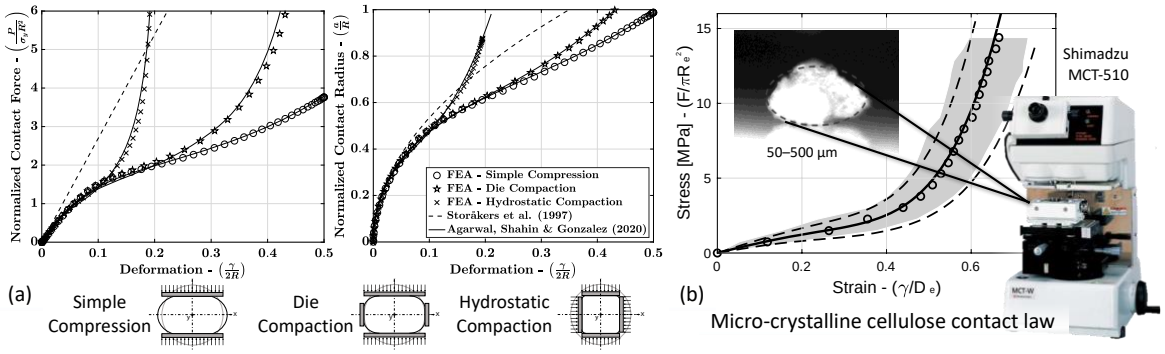


Figure 3. Mechanistic contact laws for elasto-plastic spheres at large deformations. (a) Contact force and contact radius of an elasto-plastic spherical particle under three symmetric loading configurations estimated using the mechanistic contact law by Gonzalez et al. [6, 9-10] (in perfect agreement with detailed finite element calculations) and the standard Storåkers plastic law (which is insensitive to loading configuration and, thus, inaccurate). (b) Experimentally obtained contact law for micro-crystalline cellulose particles under large deformations obtained with the Shimadzu micro-compression tester [7].

More importantly, the material properties used by these NLC formulations need to be calibrated from particle-scale experimental characterization. Specifically, two elastic and two plastic properties, and one interfacial fracture energy are needed. The Shimadzu micro-compression tester, illustrated in Figure 3b, is housed in the CP3 Characterization Lab. It effectively characterizes the force-displacement response of individual particles ranging from 50-500 μm in diameter. These particles are loaded under simple compression to large deformations and then unloaded to exhibit permanent deformations. The tester operates within a 9.8-4,903 mN force range and has a 0.001 μm displacement resolution. It is equipped with a microscope and side camera which allow for measuring three characteristic dimensions of the characterized particle. Based on the particle size and shape, the force-displacement curve can be corrected to generate the equivalent stress-strain response of a spherical particle [7]. In turn, the intrinsic variability in material properties is decoupled from particle size and shape, and the material properties pertinent to the loading-unloading path of the NLC formulation can be estimated. Inverse gas chromatography is effective in characterizing the surface energy of materials. For example, micro-crystalline cellulose (Avicel PH-200) particles have a plastic hardening exponent of 1.51, a plastic strength coefficient of 6.02 MPa, and a surface energy of 61.52 mJ/m^2. It is worth noting that despite obtaining material properties from a simple compression test, the NLC formulation can capture any other loading configurations which, in general, are much stiffer (see Figure 3a).

<u>*Proposed work*</u>: This task will extend existing NLC formulations for elasto-plastic spherical particles with bonding strength to (i) general loading configurations and (ii) dissimilar interacting particles. Solid mechanics-based NLC analytical formulations with such properties remain a long-standing open problem in contact mechanics. To broaden the range of material systems, two elasto-plastic responses amenable to analytical treatment will be considered (i) elastic-perfectly plastic [9], and (ii) rigid-plastic with power-law hardening [10]. Detailed finite element calculations will be used to validate the NLC under general loading configurations and between dissimilar particles [1,6,9-10]. <u>*Evidence for plausibility*</u>: NLC formulations for elasto-plastic spherical particles have been developed by Gonzalez et al. for symmetric loading configurations (see Figure 3a and [9-

10]). The endowment of plastic laws with bonding strength has also been proposed by Gonzalez et al. [8]. The generalization to dissimilar interacting particles has been proposed in the open literature under small deformations and unconfined loading conditions.

Risk identification: NLC elasto-plastic contact laws might not be amenable to general loading configurations in closed-form analytical expressions. *Mitigation plan*: A scheme for interpolating simple compression, die compaction and hydrostatic compaction loading conditions will be investigated as a means for approximating general configurations. This interpolation scheme might be in detriment of a very accurate treatment of powders with a wide range of particle sizes and of compacts with relative density close to one.
Risk identification: For very cohesive or stiff particles, the micro-compression testing might be unfavorable. *Mitigation plan*: Compactor simulator's compaction curves have been used to successfully estimate all material properties for *low fidelity* contact laws to predict tensile strength with no further calibration [2,4].

Task 3: Formation of strength during powder compaction
There is general agreement that solid bridge formation and attractive interfacial forces are the major contributions to strength formation. Attractive interfacial interactions are dominant under small deformations whereas solid bridge formation occurs under large deformations (see [8] and references therein). This project will restrict attention to solid bridges, which are driven by processes such as sintering, melting, crystallization of amorphous solids, or chemical reactions. A quantitative elucidation of strength formation requires not only the identification of the deformation and bonding mechanisms of interest but also of the bonding surface involved in the process. Unfortunately, it is not possible to experimentally measure the actual interfacial area that is available during tableting. However, one can assume that an upper bound for the bonding surface involved in the formation of solid bridges is the particle-to-particle contact area created during compaction [8].

State-of-the-art particle-level modeling frameworks are capable of modeling about a million particles and, thus, cannot describe all particles of powders with wide size distributions. For example, 500 mg of MCC-Avicel PH-102 powder consists of about 9 billion particles. Most of these particles are fine particles of less than 1 μm in size. On the other hand, if the particle sizes are greater than 100 μm, a 500 mg of MCC-Avicel PH-102 powder will have only about 500,000 particles. It bears emphasis that, by removing portions of the fine particles successively (d_{20}, d_{50} and d_{75}) in MCC and lactose powder, it was demonstrated experimentally that the presence of fine particles does not affect the final mechanical characteristics of the tablets, at moderate to high relative densities [12]. Specifically, peak compaction pressure, elastic recovery and tensile strength remain the same regardless of the content of the fine particles. Fine particles only affect the die-filling process and the early stages of compaction.

Thus, to model the formation of bonding strength across all stages of die compaction—die filling, compaction, unloading, and ejection—it's efficient to use a powder bed that excludes fine particles below a certain threshold (e.g., d_{50}). Next, the tensile strength of the in-silico compact can be characterized by simulating the diametral tensile strength test, i.e., by applying a compressive force along the radial direction, recording the breaking or maximum force, and calculating tensile strength from out-of-die tablet dimensions [3,11]. Interestingly, while these simulations allow for repeated testing of a single compact's tensile strength, experimental methods only permit a one-time test. This is due to the destructive nature of the diametrical compression experiment. In turn, this particle-level modeling framework can predict strength in multiple diametrical directions and elucidate the variability of strength in heterogeneous compacts, such as those with high particle-to-die size ratios [11].

Proposed work: This task will integrate the PMA and the NLC developed under Tasks 1 and 2 to effectively predict tensile strength of multicomponent blends, including the use of industrially relevant surface energy modifiers such as lubrication and coating [8]. It will also investigate the notion of fine particles not affecting the final mechanical characteristics of compacts in the context of mixtures of powders with quite different size distributions (as it is the case, for example, of micronized crystals mixed with large filler particles). It will experimentally validate this investigation following the procedure presented in [3]. *Evidence for plausibility*: This framework for predicting tensile strength has been validated for MCC, lactose [2] and copper [11] powders using *low fidelity* contact laws for elasto-plastic particles with bonding strength, i.e., using [8]. The same

framework has also been used to model all die compaction stages of powder mixtures, bilayers, and core-shell compacts [4,12].

Risk identification: Using inverse gas chromatography for particle-level measurements of surface energy might not yield accurate estimations of tensile strength. *Mitigation plan*: For each component of interest, the surface energy involved in the formation of solid bridges will be estimated from the unloading part of the compaction plot obtained using a compactor simulator. This procedure has been successful in determining surface energies for *low fidelity* contact laws to predict tensile strength with no further calibration [2,4].

Task 4: Validation and elucidation of particle-level properties and tensile strength relationships

The efficacy of the PMA to investigate powder mixtures was borne out by studying 50-50 binary mixtures of two monodisperse systems comprised by elasto-plastic particles with bonding strength. The study reveals that not only particle-level properties, but also topological differences (such as random packing, bilayer, and core-shell structures) affect the formation and evolution of the pore space and the bonding area statistical signature during compaction [4,12].

Proposed work: Building upon the foundation set by Tasks 1, 2, and 3, this task aims to delve into how tensile strength is influenced by various factors. These factors include particle-level properties (i.e., elasto-plastic properties), interfacial attributes (i.e., fracture or surface energy), topological aspects (like agglomeration or uneven mixing), and morphology (specifically, particle size distribution) in multicomponent blends compacted to medium-to-high relative densities. Two ternary systems will be studied for validation purposes, namely (**A**) MCC (2%,10%,17% by mass) as a softer elasto-plastic component, acetaminophen (APAP) as a stiffer component, and magnesium stearate as surface energy modifier (0.01-2% by mass and different mixing times), and (**B**) MCC as a softer elasto-plastic component, APAP as a stiffer component, and lactose monohydrate as a brittle component. A third system (**C**) will be used for systematically elucidating the relationship between particle-level behavior and tensile strength. A full factorial of low/high elastic, plastic, and surface energy properties will lead to N=8. Selected cases of interest with dissimilar size distributions and compositions will also be considered. Lastly, we'll **collaborate with IPFRI members** to pinpoint a fourth system, designated as (**D**). Potential considerations for this system include ceramic blends or complex geometries like catalyst supports. This system will serve two primary studies: (i) assessing strength variability stemming from particle-to-die size discrepancies and (ii) understanding the decline in out-of-die strength resulting from over-compaction. The latter specifically refers to instances where there's an excursion into the particle's elastic volumetric deformation regime (refer to Task 2 and Figure 3a). *Evidence for plausibility*: CP3 legacy experimental data for 8-mm tablets made of system (**A**) demonstrate that compaction force, elastic recovery and strength are sensitive to changes in APAP concentration and lubrication conditions (see, e.g., [14]). The analogy between accumulated damage/fracture and irreversible plasticity for highly confined brittle particles, such as lactose, has been used to estimate compaction and strength successfully [4]. This modeling framework has been used to elucidate the role of Poisson's ratio [2] and hardening plastic exponent [5] in the statistical signature of elastic and plastic, resp., particles under compaction. It has also been showed that tablets are weaker if the die-to-particle size ratio is less than 6, in agreement with ASTM D4767 [11].

Risk identification: The budget does not include any S&E nor salary for summer supervision, and it partially covers the stipend and graduate fees of a PhD student during the performance period. *Mitigation plan*: **IFPRI members** will be expected to support the project with (i) inverse gas chromatography measurements for all materials, and (ii) compaction data, strength data, and sample particles for micro-compression testing at Purdue for systems (**B**) and (**D**).

Schedule

Task	Y1		Y2		Y3	
1						
2						
3						
4						

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Response to Winter Meeting Discussion (e-mail received on February 6, 2024).

I'll start by noting that I missed an important element in the project brief - brittle fracture - so a starting question is whether you are able to include this in your proposal. Can your model approach and experimental calibration be conceptually adapted to allow for a powder developing strength through particle fracture (local disintegration and reinforcement) during compression or failure? A very commonly used pharma powder would be anhydrous dicalcium phosphate, which can develop strength above levels possible with cellulose or lactose through this mechanism.

The modeling approach and experimental calibration can be conceptually adapted to allow for particle brittle fracture and for strength development through this mechanism. The extended scope ought to be split into two sequential sub-scopes to have scientific depth and be comprised of testable hypotheses. First, as stated by the original scope of the project, a "*predictive framework for strength development in multicomponent powder mixtures undergoing cold compaction at compaction stresses large enough to cause significant plastic deformation of particles*" must be conceptualize, developed, and validated. Next, for brittle particles, the contact formulation would be endowed with a brittle failure criterion to determine, based on the particle loading configuration, the new surface area created from the formation of cracks. There is a body of theoretical and experimental work that studies particle breakage models (see, e.g., the seminal work by Wong et al. [A] that formulates a Hertzian fracture model and more recent work by Buscanera [B] that assesses the validity of a family of fracture particle models). These models relate particle size and elastic and fracture properties with fracture patterns and, thus, formation of new contact interfaces. Like the formation of bonding strength in inter-particle contact interfaces (Task 3), these new intra-particle interfaces will add to the formation of bonding strength upon further loading. In addition, the contact formulation will have to describe post-fracture behavior based on the level of confinement (e.g., the three loading configurations in Figure 3a evidently have different post-fracture behavior even if brittle). Fragments will not be modeled with new particles, but they will rather be accounted for in the loading-path dependency of the contact formulation. Lastly, the experimental component of this second sub-scope would fall squarely within Task 2 of this proposal. Specifically, the micro-compression tester is capable of measuring particle breakage events (cf. the MCC results in Figure 3b that show a dominant plastic response). In summary, particle brittle fracture is certainly relevant to strength development in powders under cold compaction and it can be conceptualized, developed, and validated as an extension of the proposed framework for plastic particles. This task is certainly the best candidate for a one-year extension of the proposed project, as it greatly leverages Tasks 1-4. A fifth material system added to those described in Task 4 would then include DCPA.

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Will there be any up-front experimental checks of to what extent the interfacial energy parameter is a function of stress/strain history for each ingredient? We are skeptical that the surface energy measured by IGC will be a useful strength predictor (due to other more dominant mechanisms). Expanding on this, can you do some of the experimental work specified in Task 4 in parallel with theoretical development to provide intuition for the latter?

This is a very good point, and Task 4 can certainly be started during the first semester of Y1. The 'risk identification' under Task 3 addresses this concern and a 'mitigation plan' is offered. The systematic elucidation of the material properties that control the tensile strength of the compacts remains a key objective of this project.

In previous IFPRI-sponsored work, there was evidence that uncontrolled humidity-induced sintering at particle contacts affected compact strength. Will you control humidity in your experiments to sufficiently low levels to avoid sintering in water-soluble components like NaCl or lactose?

The University does not have facilities that can house a rotary tablet press under controlled humidity conditions. However, the air relative humidity will be monitored and recorded during all experiments.

It would be useful for you to amplify how you plan to characterize your model powders and compacts. How will you confirm interfacial deformation and breakage? Will you be able to determine whether or not components are randomly mixed? Also, have you considered classifying your powders to create relatively monodispersed systems?

The micro-compression tester described in this proposal is the only non-traditional characterization technique. It is indeed the one that allows to characterize deformation and breakage at the particle scale, and it serves as the right tool to calibrate the proposed contact formulations. Mixing will be carried out using a Tote blender and 1-liter batches will be prepared. Proposed systems (A) and (B) have been successfully prepared in-house and a protocol is in place to attain high content uniformity. As for proposed system (D), we will work with IFPRI members to not only identify the formulation but also the right preparation protocol. The proposed predictive framework can handle polydispersity, as it has been showed in [3,4,11,13]. For example, as-received powders have been classified to understand the effect of large particles [11] and fines [13], obtaining model predictions of strength in agreement with experimental values. As suggested, considering a monodisperse system would make an excellent case study and, if there is general agreement, it might be the system of choice for (D).

You plan to use magnesium stearate in your experiments. We suggest you consider something more isotropic like sodium stearyl fumerate, which has a decently low yield stress (ca. 20 MPa) and is likely a better fit to your assumption of spherical particles.

MgSt particles are not explicitly modeled, but rather accounted for through changes in fracture or surface energy. It is worth noting that under the assumption of brittle failure mechanisms, the new intra-particle contact interfaces would have the surface energy of the unlubricated material.

Finally, we are concerned about your statement about the inadequacy of funding and the requirement that IFPRI members provide analytical support for this project. IFPRI can't speak for individual members and make this commitment for them. At this stage, we really need to know what parts of the project you can achieve with this funding alone. (If additional funding is necessary, perhaps you could consider pursuing a GOALI grant).

Additional funds have been secured since the submission of this proposal. A Ph.D. student has been recruited and awarded a teaching assistantship. During the past two semesters, the student has completed nine courses and secured a GPA of 3.93. Research under the umbrella of Task 1 is underway. The student's PhD thesis objectives are aligned with the extended scope discussed in this amendment.