The CMMC Advisory Service: Modeling Methods

Why do we model?

Modeling has become an essential part in many industrial processes. Think of CFD models which are now ubiquitous in many industries. Models for biological systems are inherently complex owing to biological complexity and variability. Yet the latter makes them also indispensable.

Many biological processes, including those in cultivated meat production, are still in a *research* stage, meaning that they need more investigation and understanding in order to get to the *design* or *optimization* stage (such as it is for CFD simulations in aeronautics).

We list here the arguments why building models is such an important step:

- Designing models means getting more insight in your system:
  - Models allow to easily combine "simple" processes into a "complex" one
  - Models allow decomposition of a complex process into simple processes.
- Models are predictive and allow simulating "what if ?" scenarios a priori to a real experiment.
- Models are generally cheap and fast to run.
- A good model can further optimize the real system and save a lot of money.

In summary, the advantage of modeling is two-fold : i) get more insight and understanding in a biological process and ii) be able to optimize and engineer the industrial applications faster.

Challenges and problems [Ongoing Discussion in Doc]

For the following challenges we assume that the primary metric of interest is cell mass / time

1) <u>Serum elimination (90% of cultivated meat companies are using serum at some stage in the process)</u>

    - Serum usage also hinders the transition to suspension adaptation for companies using suspension or cell aggregates.
    - This sounds like a problem for molecular simulations, protein folding simulations together with metabolic models. These are used in the field of medicine for drug discovery, but can also be used for media optimization and serum elimination. Example: https://doi.org/10.1002/bit.27704

2) <u>The transition from benchtop to bioreactor</u>

    - Particularly large problem for seafood.
    - *Here my first thoughts would be using CFD methods to have a priori estimates of hydrodynamic stresses and oxygenation, .. when changing the dimensions of the bioreactor.*

3) <u>For suspension adapted cells (non-microcarrier) - reattachment to the scaffold</u>

    - *Here one can propose ABM or population balance models.*

4) <u>Bioreactor designs (stirred tank vs. custom designs) + increasing oxygen / mass transfer. All these nuances vs. shear stress.</u>

5) <u>Deciding on continuous vs. batch / media recycling</u>
    - *CFD problem.*

6) <u>Migrating from small scale bioreactors to cheaper large-scale infrastructure.</u>

7) <u>Scaling up candidate cell lines</u>

8) Using 2D culture to make 3D inferences. I.e. all experiments happen at 2D and the results change in 3D.

    - *Scale-down approach, so whether we can create small scale experiments for growing cells that resemble the conditions that cells will experience in a large bioreactor. The scale-down project led by Simon Hubbard is all about this.*

9) Media formulation

10) Genetic drift - muscle tissue no longer behaves like muscle tissue after several passages. I.e. how to adapt the cells to a bio-process but retain muscle-like character.

    - *One should here make a difference between what causes the genetic drift, and how fast it propagates. As for the former, there is a selection pressure which causes some phenotypes to become advantageous. This selection pressure could be e.g. mechanical stress. In this case one could use an ABM to simulate this process over one passage. Once these mechanisms are understood, one can simulate the genetic drift over many passages with classical models (diffusion equations, random walks, ..)*

Open Questions and Remarks:

Paul:

- *Just some thoughts here in comparison with the modeling doc - I see virtually no one using RNAseq, or flux balance analysis. These would give a lot of insights on the cell physiology that could be used to tackle the challenges above. Nobody is using bayesian inference either.*
- In general, very few companies are using modeling. Some bigger ones will use CFD to design bioreactors.
- The use of AI based methods is exploding and the in silico companies offering such methods will be eager to claim they will solve any problem - and quick. How do we deal with this ?
- Being successful with a model is all about the data. The right data. Some companies will not have the right data. Or they will not share it so easily. One needs to propose alternatives , e.g. what can be found in literature. Offering literature mining of a particular problem can be of great value to a company.
- Should we only focus on meat producing companies ? What about bioprinting companies ?

- Regardless of the company's problem, what do we promise a priori ? This can range from the minimum : “we provide more insight” , to the maximum : we kill their problem.
- Work to be done: make list of companies that could have similar problems as meat companies. Best would be to make an excel sheet where we put in the companies to contact, their main activities, who to contact, and some kind of feedback. I put here the link to a sheet with some examples:

https://docs.google.com/spreadsheets/d/1dBMY5c7AYeyf9XIh1ctuXJVhyDNaBiNkiIEwAQswZ80/edit?usp=sharing

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Methods

The methods listed below are individual computational approaches to solve a particular problem. They are <u>not</u> overall solutions to a problem. In fact, many of these methods need to be combined to address a biological system of certain complexity. This is what we call a *hybrid model*.

The models are categorized in *Mechanistic* models and *Data driven* models. The former are based on first principles (such as conservation of mass, momentum, standard chemical kinetic laws, ..) and use mathematical equations such as ODEs and PDEs ; the latter are models that seek for correlations between variables using machine learning without the assumption of first principles. Both Mechanistic and Data driven approaches have their specific advantages. They can also work in a hybrid approach.

Method	General description ..	Has Been Used in the Industry To...	Challenges Method is suited to Address...
		MECHANISTIC MODELS	
Computational Fluid Dynamics (CFD)	• Simulate fluid flow, pressure, turbulence, shear stress, forces, fluid mixing *with great precision*	• Test and scale new bioreactors to determine fluid flow and optimize mixing • Optimize geometries of a bioreactor	• Detailed design of bespoke industry- and process-optimized bioreactors
Compartment Models (CM)	• Simulate material fluxes and mass balance in fixed compartments or zones (assumes homogeneous mixing) • Information may be inferred from CFD • Model with less compute power (i.e. lower cost) than CFD	• Suitable for the study of many complex systems with several objectives (system modeling, process control, scale-up...)	• Compute average concentrations of molecules or other species in parts (zones) of a bioreactor and give distribution of molecular species throughout a bioreactor run
Agent Based Models (ABM)	• Simulate behavior of complex discrete systems such as cells or microcarriers. Every cell is modeled individually and can interact with other cells.	• Understand how differences in cell concentrations influence proliferation and differentiation Understand how fluid flow interacts with cells	• Simulate cells attaching to one another as aggregates, or to microcarriers • Understand why some cell-lines work better in plates, versus bioreactors
Intracellular ODE models (IOM)	• Models to predict metabolic networks in cells, Gene regulatory networks, cell signaling, pathway modeling, etc Calculates variables continuously over time	• Predict the behavior of individual cells given known interactions with a species; e.g., given a concentration of oxygen and glucose in a bioreactor, how fast will the cell grow.	• Eliminate serum from bioprocess • Optimize media formulation to maximize proliferation Prediction of cell survival
Boolean Networks	• “Simplified” version of IOM by assuming variables have two states: “true or false” e.g. is a species or molecule or a behavior present or not? The most natural formalism to translate an influence network into a mathematical model	•Idem to IOM	• Can significantly simplfy IOM by reduction of parameters

Flux Balance	• Mathematical method for simulating metabolism in genome-scale reconstructions of metabolic networks. To reduce complexity of IOM metabolic models; however give only equilibrium steady state solutions	• Bioprocess engineering , e.g. metabolic networks of microbes used in fermentation processes	• Simulate steady state metabolic fluxes in bioreactors
		DATA DRIVEN MODELS	
Network Modeling	•Graph Convolutional Networks (GCN) are accurate and scalable biological network integration algorithm that uses a deep learning architecture to integrate many diverse and disparate biological networks. The integrated results can be used to characterize gene function and identify functional modules more effectively than any individual network alone. So called recurrent neural networks (RNNs) can estimate the effects of changes in pH and temperature in the reactor	• **BIONIC (Biological Network Integration using Convolutions)** Functional genomics to better characterize yeast genes through the integration of three functionally diverse networks, and has been used to accurately predict chemical-genetic interactions using these networks.	• To better functionally characterize genes in any organism and is especially powerful in organisms where genes are poorly characterized but networks are available. Better gene characterization in (for example) bovine cells may result in the identification of genes relevant to specific pathways related to metabolism or other processes of interest, and can be used to prioritize genes for follow up experiments.
Machine Learning and DeepLearning	• Great general interest in processes where a lot of data are generated. Used methods: Regression, classification, Data clustering, Neural networks. This approach depends highly on the availability of vast amounts of data. Black Box models: what works for one clone may not be extrapolated to another one !	• Machine learning has been extensively applied to approximate the intrinsic complexities between bioreactor operating factors (e.g. temperature, pH, substrate and contaminants concentrations, agitation and mixing times, nutrient inflow rate) and key cellular metabolisms (nutrient uptake, product synthesis). This enables (i) the estimation and prediction of important state variables (e.g. cell biomass concentration), (ii) improvements of the bioreactor's performance	• So called recurrent neural networks (RNNs) can estimate the effects of changes in pH and temperature in the reactor

		and efficiency, and (iii) monitoring the process conditions for control and safety purposes	
Hybrid Data driven -Mechanistic	A modeling technique that combines machine learning with mechanistic modeling. Hybrid models consist of a mechanistic model that accounts for the known rules and a data-driven model that accounts for the unknown rules. Every knowledge about the system, the cells or the bioreactor is inserted into the mechanistic part (mass balances, ordinary differential equations describing growth ..) and the unknown parameters are estimated by an machine learning algorithms.	to model cell behavior in different environmental conditions. In combination with model-based or intensified Design of Experiments up to 70% of the lab experiments can be reduced. The advantage of using hybrid models to describe cellular growth and product formation was already successfully demonstrated for CHO, HEK, and E coli cultures.	In combination with CFD modeling to even better describe the cellular behavior based on input parameters. Currently input parameters like temperatures, pH, media compositions were already successfully described. In combination with CFD information (shear constrains or mixing time information, or gas concentration information) even better and more transferable (scale-up) models can be expected. The combination of iDoE or mDoE with hybrid modeling can help the cultured meat industry to significantly reduce experimental effort to identify the ideal process conditions. First-principle knowledge in the form of simplified differential equations (e.g. mass and energy balances) have provided mechanistic structure to ANN in the form as hybrid models by [80] for state estimation and prediction in a fed-batch stirred tank bioreactor.
Image Analysis	• **Image analysis** and, in particular, **image segmentation** refers to algorithms that are able to identify various regions of interest in a two-dimensional image. Typically, some initial training from domain experts is required for the algorithms to be able to recognize such regions or specific features of the image. Image segmentation.	• H**as been used** extensively in digital pathology, particularly for H&E histology images, but also in multispectral imaging in which cellular markers are labeled by different colors. An example of such image segmentation is the automated identification of tumor regions as well as tumor-infiltrating lymphocytes[1] and other immune cells. In the	• C**an be used** to identify cells of interest growing in a tissue, such as myocytes, adipocytes, and other cell types, as well as their spatial relationships, such as proximity to each other. The advantage of such methods is that the results are objective and reproducible and do not rely on visual quantification by an expert, which becomes impractical for large

		context of cultivated meat, such algorithms.	numbers of images.
RNA Seq Analysis	• RNA-Seq nucleic acid sequencing reveals the transcriptomic (RNA transcript) profile of a biological sample at a given moment, revealing expressed genes and their level of expression. RNAseq provides a biological "snapshot" at a particular point in time/condition.	• RNAseq has been used across disciplines as 1) a way to map expressed genes for a particular biological sample and 2) as a comparative tool. Differential expression reveals the genes that are up and down regulated when two states are compared. For instance, RNAseq deployed on a control vs. stress state might reveal which genes when up or down-regulated play roles in stress response.	• For cultured meat, these two applications are certainly still useful. RNAseq can also be deployed to assess metabolic and other key pathways which could be important for genetic engineering of cell lines and/or for media design or comparison.

Detailed Descriptions of Modeling Methods

Mechanistic modeling

Mechanistic models are represented by methods based on first principles, such as conservation of momentum, mass, energy, mass action laws, and so on. To describe the time evolution of the system one uses equations of motion which are solved numerically. The equations are parametrized and those parameters usually have a physical meaning. This type of modeling approach gives a profound insight into the problem as we understand the *mechanisms* behind it.

CFD (Computational Fluid Dynamics)

A collection term for numerical methods to simulate fluid flow and related physical properties and effects like pressure, turbulence, shear stress, forces, fluid mixing. CFD is well established in aeronautics and automobile industries, yet it is also finding its way in biological modeling.

Has been used CFD is, amongst others, applied to study mixing , mass transfer and substrate gradients . CFD is used extensively in industry already to simulate mixing in bioreactors, for example for yeast fermentation. Also used a lot in the automotive and airplane industry to investigate the aerodynamics of vehicles.

Can be used in cultivated meat to test new designs and scaled up bioreactors for their mixing efficacy and to determine fluid stresses, but also for the flow of fluid through scaffolds/tissues and the effect of small scale turbulence on cell deformation.

Link to reference work on this method :
https://www.sciencedirect.com/science/article/pii/S1369703X21003417

(Nadal-Rey, 2021)

Compartment models (CM)

CM is a collection of models that predicts the state of the system as variables in time. In contrast to CFD, the spatial component of these variables are discarded.

CM are nowadays frequently used in PharmacoKinetics/dynamics, in which the compartments are the organs in an organism and the species are the drugs/molecules.

The advantage of CM is their relatively small computational cost. They can replace the costly CFD simulations if their parameters are well estimated. For example, while in CFD one could model the complete spatial-temporal evolution of the bubbles in a bioreactor, a CM will first define "compartments" , these can be fixed locations in a bioreactor. Each of these compartments has a fixed volume. For each compartment one will compute how much of a species (bubbles, carriers, ..) is entering, how much is leaving, how much has been produced, and how much has disappeared. This gives an actual count of the bubbles in the compartment at each time, assuming that the bubbles in the compartment are homogeneously distributed.

Link to reference work on this method :

Population Balance models (PBM)

PBM are somewhat related to CM, but they can be seen as an extension. In PBM one also takes into account other variables, such as the size of the species.This can be important, as e.g. one would like to know not only how many bubbles there are in the bioreactor, but also what their size is. PBM would take into account what happens if bubbles collide and aggregate to a larger bubble or instead split up into smaller ones.

PBM are used in chemical engineering systems describing particulate systems (e.g. in coagulation processes)

Link to reference work on this method :
https://www.sciencedirect.com/science/article/abs/pii/S1369703X18303127

(Haringa et al, 2020)

ABM (Agent Based Modeling)

Modeling technique where the actions and interactions of autonomous agents that are defined by a set of behavioral rules are simulated to explain the behavior of the complete system. Useful for studying systems that consist of many similar self steering subparts that interact with their environment and other subparts.

Has been used in ecology, psychology and sociology to study the behavior and emergent properties of groups of organisms (agents). Energy system and economic simulations where actors in the energy grid economic network are considered as agents, and the effect on the whole energy chain and society is studied.

Can be used to model biological cells as agents and simulate their reactions with each other and the culture conditions, both in proliferation and differentiation (tissue formation) bioprocess stages to design/optimize the bioprocess. Can also be used to look at the future supply chain and economic/market implications and LCA, in these cases, the agents would be meat production facilities, conventional agriculture farms, feed producers, consumers and other players in the meat supply chain.

Link to reference work on this method :
https://link.springer.com/article/10.1007/s40571-015-0082-3

(Van Liedekerke et al, 2015)

Intracellular ODE models

By this we mean all the model types that explicitly predict the time evolution of concentrations of molecular species or other variables in a cell. Gene regulatory networks (*GRNs) described by (large) ODE systems can describe such time evolutions.*

Has been used They are ubiquitous in systems biology and used extensively. They can treat metabolic networks, Gene regulatory networks, cell signaling, pathway modeling, etc. Usually these are highly coupled systems, meaning that one needs to solve many variables at the same time. These models usually also contain a lot of parameters.

Can be used to predict the behavior and fate of individual cells given one knows the interaction with a species. For example, given one knows the concentration of oxygen and glucose in a bioreactor, how fast will the cell grow.

Link to reference work on this method :
https://link.springer.com/article/10.1007/s41965-020-00046-y

Boolean networks

These models try to treat the same problems as the continuous methods, but truncate all variables to TRUE or FALSE., ie a species or a behavior is present or not. They are less complicated than ODE models. They allow to identify oscillations, multi-stationary events, long-range correlations, switch-like behavior stability and hysteresis in GRNs.

Has been used Often used in systems biology (bacteria as well as mammalian cells), because they introduce a great deal of simplicity. Can also be combined with the continuous models.

Can be used Can be used as a first approach to model a system, because the number of parameters to determine is much smaller than for continuous systems.

Link to reference work on this method :
https://link.springer.com/article/10.1007/s41965-020-00046-y

Flux balance

Mathematical method for simulating metabolism in genome-scale reconstructions of metabolic networks. FBA is based on the stoichiometric matrix and a biologically important objective function for identifying optimal reaction flux distributions which are subsequently used to unravel the metabolic capabilities of the studied system. In contrast to ODE models, these models assume steady state behavior of concentrations in the cell (no dynamics) which greatly reduces computational costs.

Has been used Bioprocess engineering , e.g. metabolic networks of microbes used in fermentation processes.

Can be used Simulate steady state metabolic fluxes in bioreactors.

Link to reference work on this method :
https://web.archive.org/web/20080201124026/http://www.nature.com/nbt/web_extras/supp_info/nbt0201_125/info_frame.html

Data Driven modeling

In contrast to mechanistic methods, data driven models do not use first principle laws. Instead They try to find correlations between data sets using classical statistical techniques or neural networks. They have a great general interest in processes where a lot of data is generated.

Data drive models can be black Box: what works for one clone may not be extrapolated to another one !

Network modeling

Has been used Has been used in functional genomics to better characterize yeast genes through the integration of three functionally diverse networks, and has been used to accurately predict chemical-genetic interactions using these networks. Machine learning has been extensively applied to approximate the intrinsic complexities between bioreactor operating factors (e.g. temperature, pH, substrate and contaminants concentrations, agitation and mixing times, nutrient inflow rate) and key cellular metabolisms (nutrient uptake, product synthesis). This enables (i) the estimation and prediction of important state variables (e.g. cell biomass concentration), (ii) improvements of the bioreactor's performance and efficiency, and (iii) monitoring the process conditions for control and safety purposes.

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So called recurrent neural networks (RNNs) can estimate the effects of changes in pH and temperature in the reactor

Example: Graph Convolutional Networks (GCN)

> **BIONIC (Biological Network Integration using Convolutions)** An accurate and scalable biological network integration algorithm that uses a deep learning architecture to integrate many diverse and disparate biological networks. The integrated results can be used to characterize gene function and identify functional modules more effectively than any individual network alone.
>
> **Link to reference work on this method :**
> https://www.biorxiv.org/content/10.1101/2021.03.15.435515v2

Image Analysis

Image analysis and, in particular, image segmentation refers to algorithms that are able to identify various regions of interest in a two-dimensional image. Typically, some initial training from domain experts is required for the algorithms to be able to recognize such regions or specific features of the image. Image segmentation.

Has been used extensively in digital pathology, particularly for H&E histology images, but also in multispectral imaging in which cellular markers are labeled by different colors. An example of such image segmentation is the automated identification of tumor regions as well as tumor-infiltrating lymphocytes[1] and other immune cells. In the context of cultivated meat, such algorithms.

Can be used to identify cells of interest growing in a tissue, such as myocytes, adipocytes, and other cell types, as well as their spatial relationships, such as proximity to each other. The advantage of such methods is that the results are objective and reproducible and do not rely on visual quantification by an expert, which becomes impractical for large numbers of images.

Link to reference work on this method : https://pubmed.ncbi.nlm.nih.gov/29617659/

(Saltz et al, 2018)

Hybrid mechanistic - Data driven models

Cells interact and move through contact with ECM and other cells. These generate forces that modify the cells' position or mechanical state. Such a behavior can be well described by, for example, CFD or Agent based models. On the other hand, these forces directly or indirectly can modify the cell state.

Such a cell state can be modeled through a GRN. However, the relationships in and between cell states are generally complex to establish. Therefore, determining the dynamical responses of cells temporarily remains with a mathematical set of equations an obscure task.

A solution to this is to use hybrid mechanistic - data driven approaches. In this approach, we combine the output mechanistic models (CFD, agent based) with machine learning or deep learning techniques that try to predict the cell state without using parameters that fix transitions or the kinetic rate constants.

Has been used [describe how this technique has been used in industry or science]

Can be used [give examples how we think this technique can be used for cultivated meat]

Link to reference work on this method: https://doi.org/10.1016/j.bej.2021.108054

Data driven modeling/techniques - Ousmane will email the network

Machine Learning - Ousmane will email the network

Deep learning - Ousmane will email the network

The deep learning research community has a strong norm of open source models; interested practitioners are encouraged to explore the models available on, e.g. Hugging Face.

Probabilistic modeling -> Bayesian modeling - Ousmane will email the network

Many data-driven modeling approaches ignore the uncertainty inherent in data collection and curation by hoping that errors cancel out at large enough scales. By contrast, probabilistic models the uncertainty explicitly via a probability distribution. As we will see, accounting for uncertainty in a precise way allows scientistis and practitioners to make data-driven decisions in a more rigorous fashion, with impressive results.

Image Analysis (segmentation) - Ousmane will email the network

Image segmentation is usually either semantic (labeling portions of an image as car, road, sidewalk), instance (draw an outline around all of the people in an image), or both (Minaee et al 2021). State of the art algorithms vary depending on the application, but typically involve a variant of a Convolutional Neural Network (CNN). CNNs are particulary suited to image analysis because they leverage the semantic similarity between nearby regions of an image. Practioners with limited datasets can fine-tune a number of open source models for their particular task (see the Hugging Face repository for image segmentation; Hugging Face is an open source software collective for deep learning models).

Image reconstruction - Ousmane will email the network

Image reconstruction is an example of an *inverse problem* in imaging; it is so-called because one typically is inverting a function applied to an image, e.g. adding color to a grayscale image, or upscaling a low-resolution image. Deep learning is the workhorse of this field and has had spectacular successes in medicine and life sciences applications, such as in MRI, CT, PET, and SPECT images (Ongie et al 2020). A state of the art method is based on Deep Generative Models, which leverage deep neural networks (especially Convolutional Neural Networks) to learn an efficient low-dimensional representation of an image manifold through data. Just as a deep learning model for a *forward* problem might be called "data-driven compression," the deep networks here may be thought of as "data-driven de-compression." Active Learning & Design of Experiments

Active learning is a data-driven method for predicting what set of physical experiments would give the greatest possible "information" about a phenomenon of interest. It is an extension of the well-known Design of Experiments setup, which does the same thing but in a single set of (concurrent) experiments.

Cosenza et al. 2022 apply AL techniques to cell culture media design for growth of C2C12 cells. They use a Bayesian optimization algorithm, which maintains a probability distribution over some outcomes and iteratively updates the distribution as more and more data arrive. The goal is to reduce overall experimental cost by incorporating all available measurements in a statistically optimal way. In the cited work, the authors use Bayesian optimization to design a media for 181% greater growth of C2C12 cells, and with 38% fewer experiments, than a design-of-experiments method.

Bournazou et al 2016 extend this paradigm even further by optimizing batch-fed growth of E. coli using robotic feeders and a continuous online optimization process, based on a differential equation growth model. This work is notable for pushing the "automate, optimize, validate" framework of bioprocess design much further than most other researchers. In particular, they achieve a coefficient of variation 50 times lower than the baseline sequential experimentation method, for the same amount of physical resources; this demonstrates the dramatic bioprocess improvements possible with relatively crude statistical methods.

RNA-seq analysis - Sandra/Rebecca/Jaro

DNA > RNA > protein. The transcriptome is the set of RNA transcripts in an individual or a population of cells. RNA-Seq nucleic acid sequencing to reveal the the transcriptomic profile of a biological sample at a given moment, revealing expressed genes and their level of expression. Gene-expression profiles are very sensitive to perturbations in physiological conditions. RNAseq provides a biological "snap shot" at a particular point in time/condition. Traditionally, RNAseq has been used across disciplines as 1) a way to map expressed genes for a particular biological sample and 2) as a comparative tool. Differential expression reveals the genes that are up and down regulated when two states are compared. For instance, RNAseq deployed on a control vs. stress state might reveal which genes when up or down-regulated play roles in stress response. For cultured meat, these two applications are certainly still useful. RNAseq can also be deployed to assess metabolic and other key pathways which could be important for genetic engineering of cell lines and/or for media design.

Link to reference work on this method :

https://www.cytivalifesciences.com/en/us/solutions/bioprocessing/products-and-solutions/upstream-bioprocessing/single-use-bioreactors/digital-bioreactor-scaling-tool?extcmp=cy22396-global-bp-free-bioreactorscalertool-organic-social-sm-lie-bsr4

Optimization - Paul/Jaro

- Genetic algorithms (e.g. CMA-ES)
- Bayesian approaches
- Frequentist approach (max likelihood)

Reduced order Modeling - Paul/Jaro

- Surrogate models (e.g. Polynomial chaos)

Domains

- Physics
  - Fluids
  - Cell mechanics
- Biology
  - Multicellular organisation
  - Propagation of mutations / Selection pressure
  - Metabolics
  - Gene regulation
  - Molecular interactions
-

Points to discuss

- Who are the target companies ? Make a list ? Which ones to exclude , ..
- Target person to contact . What is the ideal profile ? Which media to use : email, linkedin, ..
- If contact is established, have a list of points to discuss

- Next step… Can we explain in a few lines what these methods are… What is this method? How can it be applied in the industry? How could we use it in cultivated meat?
- Can we use the GFI process-like diagram to explain where they can be applied? Ousmane to email Elliot asking for this https://gfi.org/science/the-science-of-cultivated-meat/deep-dive-cultivated-meat-bioprocess-design/
- Also, we will send the document to the community so they know what we are planning to work on and volunteer

- Next steps… Paul thinks 'data driven' methods are a whole world on its own. Therefore it needs to be fleshed out even more.
- Maybe add a summary graphics in the beginning
- Paul thinks the problems should actually open the document,
- So Ousmane's suggested plan: intro, vision, challenges (summary), available methods, call for scientist with expertise in those methods