IMPROVING SAMPLING EFFICIENCY IN ^{13}C MFA

Master's Thesis Outline

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CHALLENGES IN INST ^{13}C MFA

- A forward simulation is a map from the flux polytope U to the isotope labelling space I.
- The mass balance equations $\frac{\mathrm{d}}{\mathrm{d}t}x = g(u,t)$ give us the time derivatives of the isotope labellings $x \in I$
- In isotopical stationary state

$$\frac{\mathrm{d}}{\mathrm{d}t}x = 0$$

- In isotopical instationary state, measurements come with timestamps t_0, hence

$$x(t_0) = \int_0^{t_0} g(u,t)\,\mathrm{d}t$$

- Integration is computationally more costly than solving $\frac{\mathrm{d}}{\mathrm{d}t}x = 0$, **up to two orders of magnitude** $\rightarrow$ 1 day vs 3 months

SAMPLING INST SCENARIOS

- Sampling INST scenarios is hence very costly, since for every move the forward simulation has to be computed.
- Even for rejected moves!
- Natural target: **Minimize the number of forward simulations**

What can we do?

A FIRST NAIVE THOUGHT

- Use chain history to fit a model online
- Use the model to get a gradient estimate
- Use this cheap gradient for tuning proposals

→ **not Markovian anymore!**
However, it contains some known concepts

MULTI-STAGE MCMC

- Replace costly evaluations with cheap but less accurate ones
- Only compute exact results, if the move was accepted by the cheap model
- Else stay put

- Adapt proposal probability
- Allows for stacking of arbitrary many intermediate acceptance steps
- **What kind of cheap models do we have?**

CHEAP MODELS

- INST vs stationary scenarios:
  Every flux distribution satisfying the instationary data should also satisfy the stationary one
  $\rightarrow$ Problem: we don't have mixed data
  $\rightarrow$ But we may extrapolate from instationary data to stationary one

- Increasing error threshold using adaptive solvers for forward simulations:
  $\rightarrow$ How do inaccurate simulations affect the certainity?
  $\rightarrow$ Also this requires global error estimates

CHEAP MODELS

- Incomplete vs complete simulations
  → Omitting some isotopomer measurements might reduce the network size and hence the system

- Regression models vs simulations
  → No data to fit the model on
  → Generating data is costly and should match the target function
  → *the chicken or the egg?*

TRUST CRITERION APPROACH

- Muller et al.[1] propose a trust criterion to use a *fishy* model fitted on a pre-run
- If the fishy model rejects too often, switch to exact evaluation
- If the exact evaluation matches the fishy model often enough, switch back to fishy only

- This approach may be generalized to any regression model
- The usage of the fishy model is arbitrary as long as we trust it
  - Tune proposal distribution
  - Apply Multi-Stage MCMC step
  - Gradient-based proposals
  - ...

[1] A neural network assisted Metropolis adjusted Langevin algorithm. https://doi.org/10.1515/mcma-2020-2060

ACTIVE SUBSPACE METHODS AND ADAPTIVE MCMC

- Active Subspace Methods
  - Identify subspaces with largest influence on the target function
  - Also identify non-identifiabilites

  $\rightarrow$ Reduce dimensionality of our parameter space

- Adaptive MCMC
  - Tune proposal distribution
  - Use the whole chains history

  $\rightarrow$ **not Markovian anymore!**

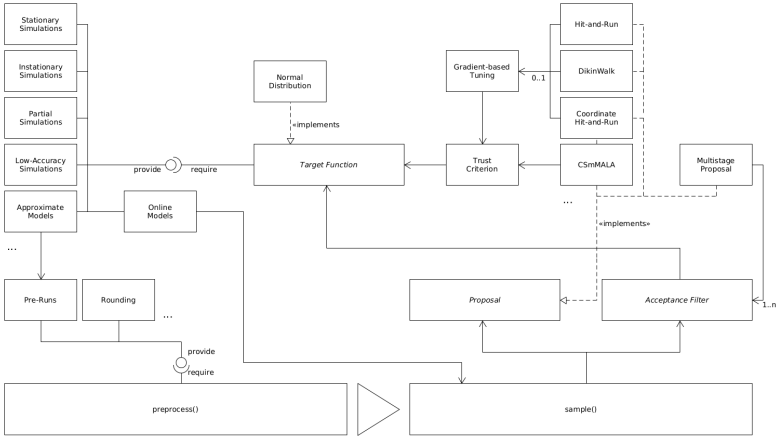
  $\rightarrow$ Applying online methods takes additional care to guarantee convergence

  ... Most probably beyond scope of a Master's thesis

THE FRAMEWORK

- The different parts described here are mostly combinable, which calls for a framework

THE FRAMEWORK



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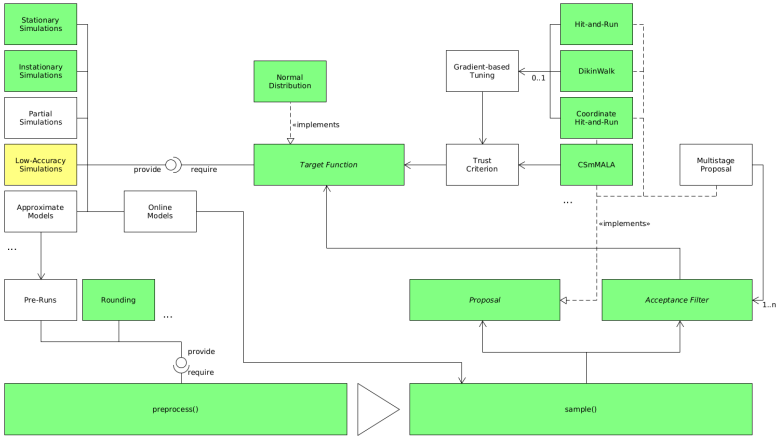
THE FRAMEWORK

The current status



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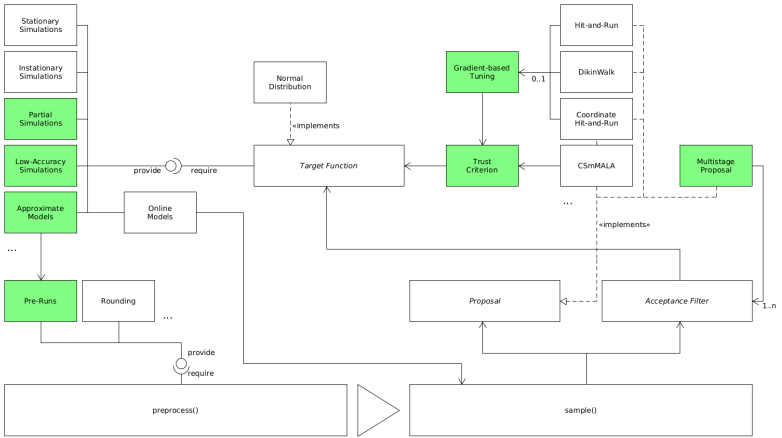
THE FRAMEWORK

Scope of this work



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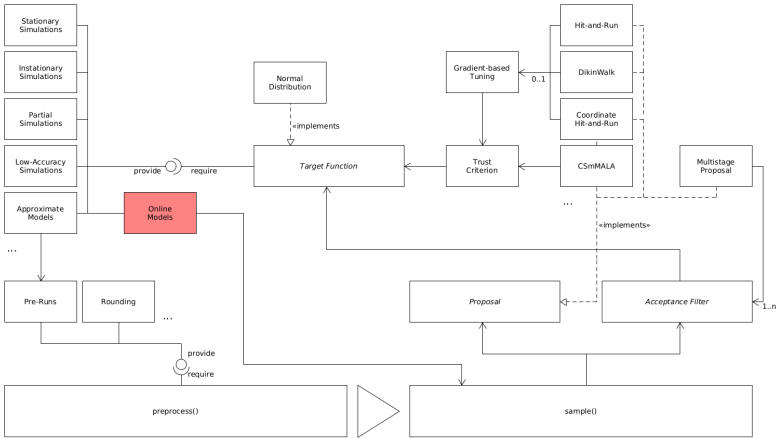
THE FRAMEWORK

Most probably beyond scope



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ACTION PLAN & GOALS

- Start off with proof of concept
  - Implement general framework
  - Use dummy simulators with artifical noise and delays
  - Test approximate models and trust criterion approach with them too

- Develop guidelines for meaningful and effective use of the framework
  - How many stages? And what coarse models?
  - Length of pre-runs? Perform pre-runs at all?
  - What proposal moves go well with multi-staging?
  - Where to use fishy models?
  - Trust criterion parameters?
  - . . .

Thanks!