Does It Pay Off to Explicitly Link Functional Gene Expression to Denitrification Rates in Reaction Models?

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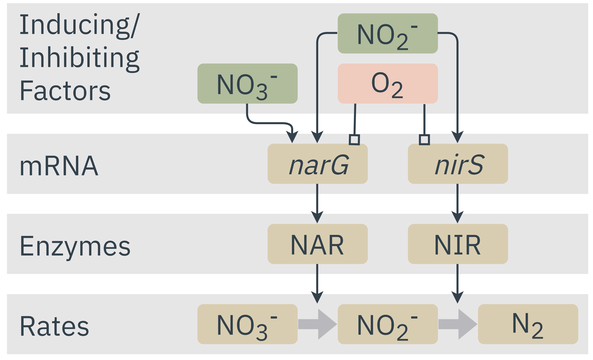
Why Use Molecular Biological Data for Modelling?

- It provides quantitative information about microbial
  - abundance,
  - activity, and
  - metabolic function.
- More and more data is available and could improve our understanding of nitrogen cycling. However, predicting environmental turnover requires quantitative understanding of reaction rates.

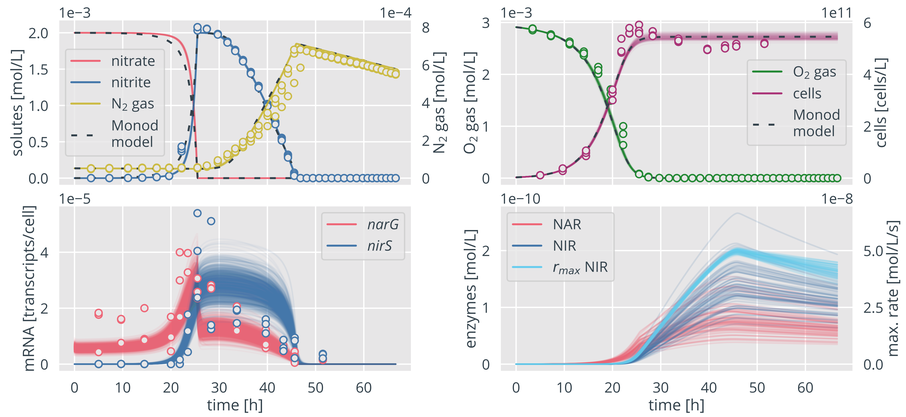
➔ We need to develop models that link molecular biological data to turnover rates.

Modelling Approach



- Simulating batch experiments inoculated with *Paracoccus denitrificans*, oxidizing succinic acid coupled to aerobic respiration and denitrification.[1]
- Bayesian approach (Sequential Monte Carlo) for parameter estimation and uncertainty quantification. [2, 3]
- We compare our transcript-enzyme based model with a standard Monod type formulation and test potential simplifications.

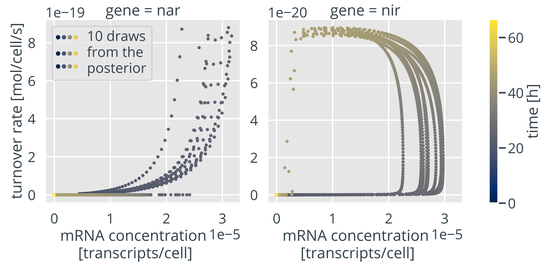
Enzyme Based Simulation vs. Monod Model



The figure shows 50 draws from the posterior of the enzyme based model (all panels) and the posterior median of the Monod type model (upper two panels).

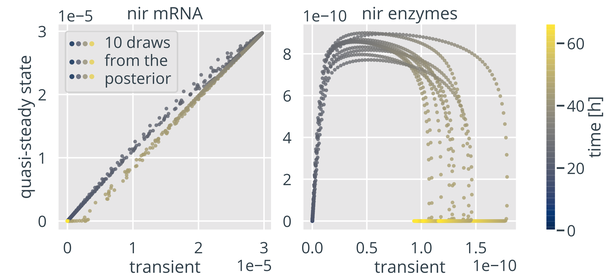
- Nitrogen species, oxygen and cell densities (upper panels) are simulated accurately by both, the transcript-enzyme and Monod model formulations.
- The timing of the dynamics of gene expression are captured, however, with larger uncertainty.
- Posterior enzyme concentrations exhibit a wide spread but the maximum rate of NIR (enzyme concentration × enzyme efficiency) is well determined.

Transcript-Rate-Relationship



Strong hysteresis between transcript concentrations and reaction rates implies that transcript concentrations cannot be used as a proxy for rates in a simplified model.

Quasi-Steady State Assumption



- Fully transient mRNA concentrations match the quasi-steady state concentrations very well.
- Enzyme concentrations deviate significantly from the quasi-steady state concentrations with a strong hysteretic behaviour: Quasi-steady state is not a valid assumption for enzymes.

Conclusions

- Modelling gene expression dynamics allows for quantitative predictions about transcript concentrations, but does not improve rate predictions.
- ✖ The process based rate formulation cannot be replaced with a direct relationship to transcript concentrations under the experimental conditions.

References

[1] Zhi Qu et al. “Transcriptional and Metabolic Regulation of Denitrification in *Paracoccus denitrificans* Allows Low but Significant Activity of Nitrous Oxide Reductase under Oxic Conditions”. In: *Environmental Microbiology* 18.9 (2015), pp. 2951–2963. DOI: 10.1111/1462-2920.13128.

[2] John Salvatier, Thomas V. Wiecki, and Christopher Fonnesbeck. “Probabilistic Programming in Python Using PyMC3”. In: *PeerJ Computer Science* 2 (2016), e55. DOI: 10.7717/peerj-cs.55.

[3] S. E. Minson, M. Simons, and J. L. Beck. “Bayesian Inversion for Finite Fault Earthquake Source Models I—Theory and Algorithm”. In: *Geophysical Journal International* 194.3 (2013), pp. 1701–1726. DOI: 10.1093/gji/ggt180.

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