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Multiscale Modeling of Circadian Rhthyms Of the model organism *Neurospora Spora*

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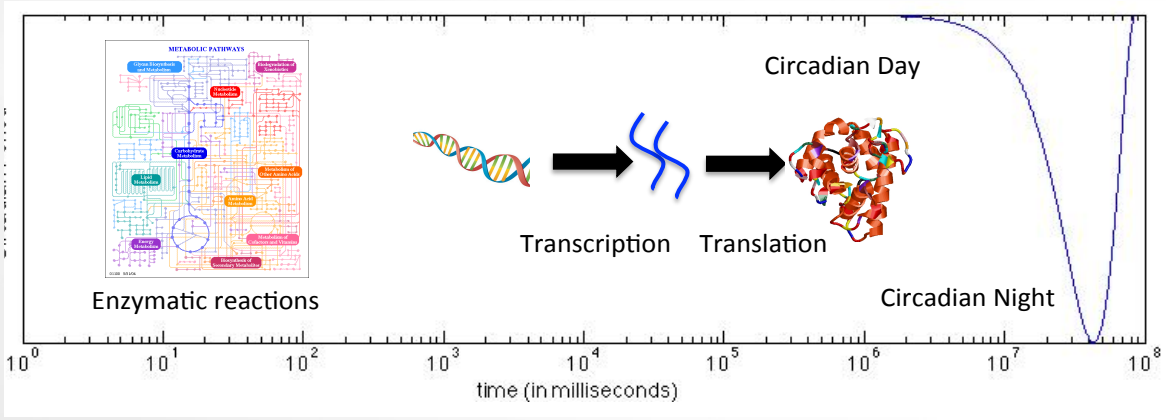

Purpose and Intended Use of Models

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- Math: New ODE formulation of the law of mass action based on statistical thermodynamics
  - Formulate an ODE that uses chemical potentials instead of rate constants.
  - Expand and collapse time scales as needed by making steady state the reference state, enabling the use of operator splitting to model different timescales.

- Intended Use:
  - Modeling of cellular metabolism
  - Modeling of metabolism and non-metabolic process such as regulation and protein expression.
  - Two Use Case scenarios
    1. Experimental data on metabolite concentrations are available.
    2. No data available – uses a maximum entropy production rate assumption

- In principle, (1) can be used for any sets of coupled reactions, but not (2).

Key Components of the Model Credibility Plan

- Mathematical Model
  - Uncertainties in chemical potentials (parameters)
    - Dependent on cytoplasm solvent properties
  - General impact of uncertainties of chemical potentials on reaction rates.

- Biological Model
  - Impact of parameters on cell dynamics, specifically the time dependence of
    - the metabolic reactions,
    - regulation and
    - clock time.
  - Use case scenario 2: Characterize impact of maximum entropy production rate assumption on replication energetics and natural selection.

Timeline and milestones of the Model Credibility Plan

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- Will test in final year. Could test mathematical model sooner.
  - Two evaluations
    - Matlab script for simple mathematical model to test general concept
    - Python motebook and/or C library for biological model using same math.
- 3 weeks of funding for credibility testing for a third party
  - We expect that the testing actually take less time.
- Flexibility to barter within the MSM consortium such that we could fund ourselves to evaluate the credibility of others models in exchange for others funding themselves to test ours.

Year 1 progress of the Model Credibility Plan

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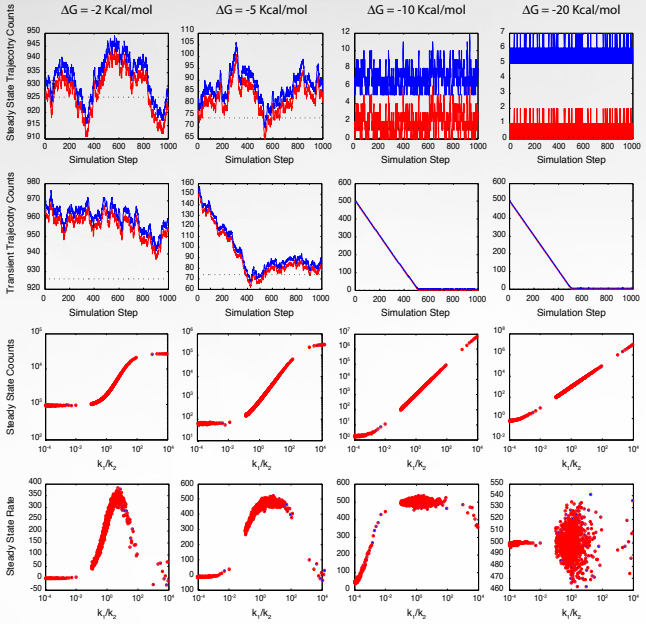
- Evaluated parameter space for a simple coupled reaction.



- Scaling up to full model:
  - Discussed Uncertainty Quantification with DOE Center on Uncertainty Quantification
  - Ensemble modeling using a Monte Carlo choice of parameters still seems like good way to go.
  - Others:
    - Bayesian modeling
    - Computational Singular Perturbation Analysis
    - Circadian Response Analysis

Challenges and opportunities: Biological Validation

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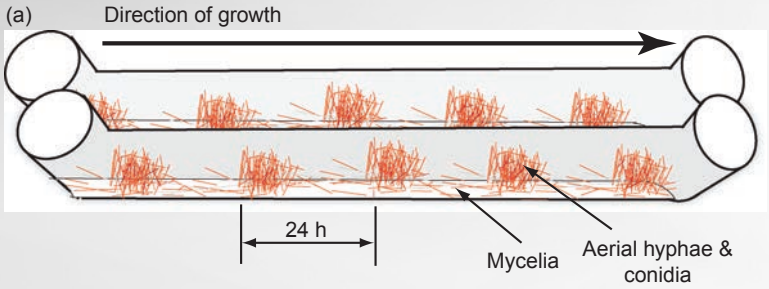
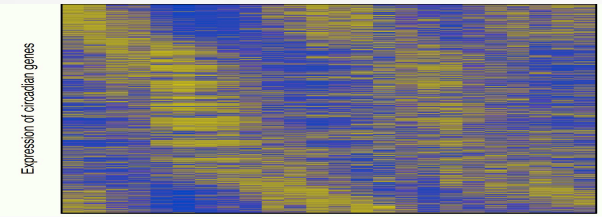
- Opportunities: Proteomic state
  - Proteomic state: key clock proteins can be measured.
    - Are simulations and experiments congruent?





- Challenges: Metabolic state
  - Getting experimental data: C13 Metabolic fluxes from a filamentous fungi
  - Chemostat with filamentous fungi is problematic.
  - Alternate validation:
    - Comparing simulations with experimental clock protein data.
    - E. coli MFA
- Working with Wayne Curtis (Dept. of Chemical Engineering, PSU) on metabolic flux analysis.

Uniqueness of the Model Credibility Plan

- (Hypothesis) Evaluation of maximum entropy assumption also provides insight into natural selection.
- Hope to team with DOE SciDAC Institute for uncertainty quantification.

Crossover with Credible Practice of Modeling & Simulation in Healthcare

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Mathematics & Computation Team

4 responsive members
forum discussion
alternatives, clusters, additions
individual member ranking
listing of 3 most important rules
group ranking
non-linearly weighted scoring

first 10 shown

- Use competition of multiple implementations to check and balance each other.
- Document your code and make your code readable.
- **Explicitly identify experimental scenarios illustrating when, why, and how the model is false (alternative: Explicitly list your limitations).**
- Make it easy for anyone to repeat and/or falsify your results (alternative: Make sure your results are reproducible).
- Use traceable data that can be traced back to the origin.
- Use version control.
- Define your evaluation metrics in advance.
- Practice verification / validation / uncertainty quantification (alternative: attempt verification within context).
- Define the use context for which the model is intended.
- **Develop with the end user in mind.**

Users Team

4 responsive members
e-mail response by individuals
individual member response
clustering of rules in relation to each other
listing ten important rules without ranking
group ranking
frequency of rules emerging in individual lists (separately or within a group)

first 10 shown

- **Define the context the model is intended to be used for.**
- Disseminate whenever possible (source code, test suite, data, etc).
- Use appropriate data (input, validation, verification).
- Provide examples of use.
- Get it reviewed by independent users/developers/members.
- Use version control.
- Attempt uncertainty (error) estimation.
- **Explicitly list your limitations.**
- Perform appropriate level of sensitivity analysis within context of use.
- Attempt verification within context.

Standards & Guidelines Team

7 responsive members
forum and e-mail discussions
no explicit individual member ranking
group ranking
synthesis into 10 general themes by consensus
weighing based on majority feedback

- Plan and develop the M&S with the intended purpose/context, as well as the end-user in mind.
- Use appropriate data (input, validation, verification).
- Test the M&S appropriately within context (verification & validation, uncertainty quantification, sensitivity analysis, test cases).
- Document important elements of the M&S (domain of validity/invalidity, intended use, users' guide, code documentation, etc.).
- Explicitly list your limitations.
- Have the M&S reviewed by independent users/developers/members.
- Use version control.
- Use appropriate discipline specific guidelines and standards.
- **Use consistent terminology or define terminologies.**
- Dissemination of the M&S.