

Fully Automated Attractor Analysis of Cyanobacteria Models

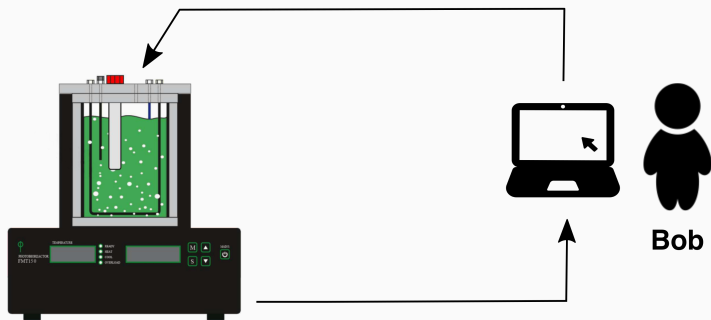
Nikola Beneš, Luboš Brim, Jan Červený, **Samuel Pastva**, David Šafránek, Jakub Šalagovič, Matej Troják

Faculty of Informatics, Masaryk University, Brno, Czech Republic

Control of cyanobacteria in a photo-bioreactor

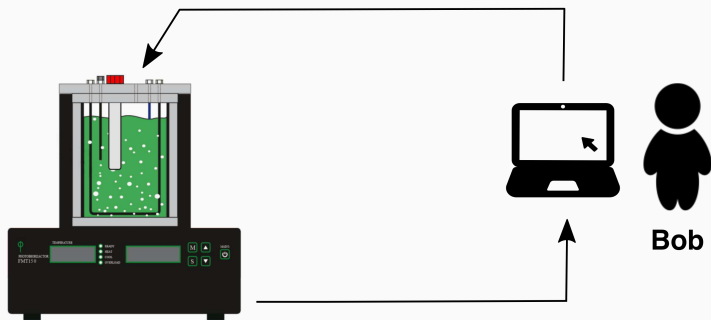
Motivation: Cyanobacteria control

Control of cyanobacteria in a photo-bioreactor



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Control of cyanobacteria in a photo-bioreactor



Model-based control \Rightarrow e-cyanobacterium.org

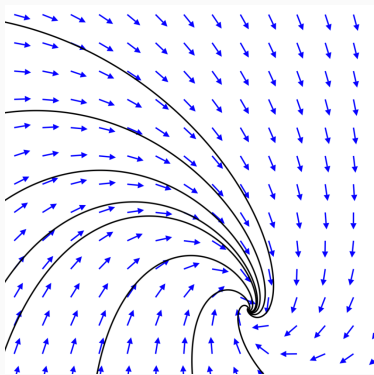
Problem: Attractor localisation with parameters

- Non-linear complex biological ODE models
- Parameter tuning controls attractors

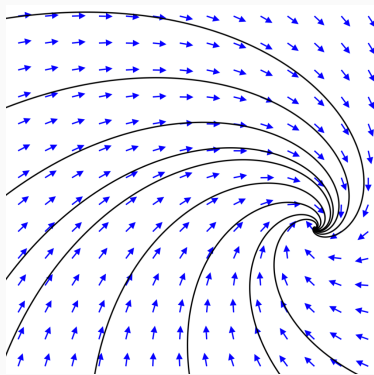
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$\rho = 0.4$



$\rho = 1.0$



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- Simulation, sampling, continuation

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- Depend on the type of the system
- Requires a skilled model analyst
- Computationally intensive, but hard to parallelise

Method: Terminal strongly connected components

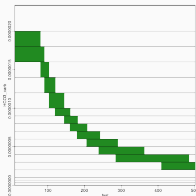
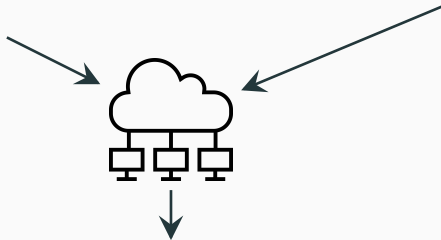
$$\frac{dx_1}{dt} = f_1(x_1, \dots, x_n)$$

$$\frac{dx_2}{dt} = f_2(x_1, \dots, x_n)$$

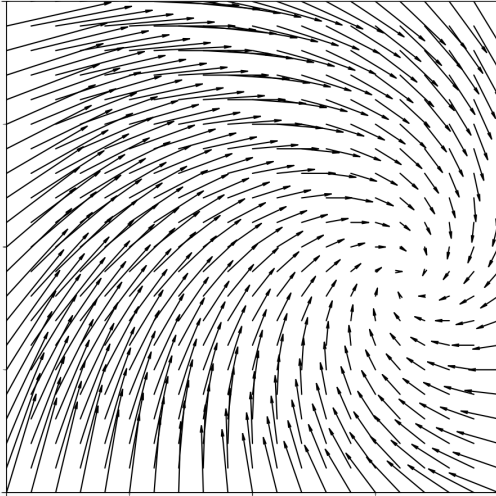
⋮

$$\frac{dx_n}{dt} = f_n(x_1, \dots, x_n)$$

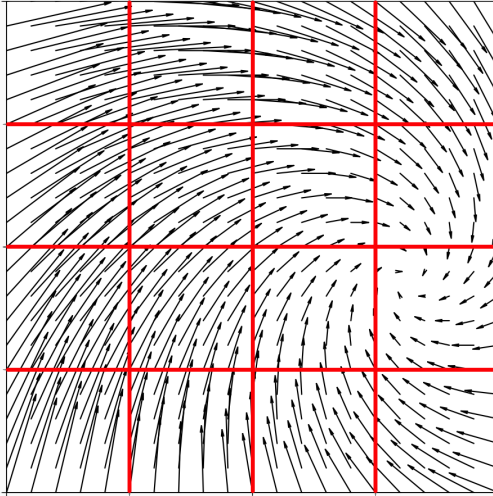
Run Attractor Analysis



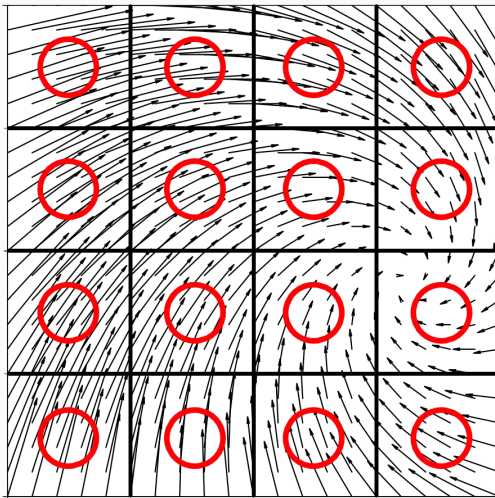
Method: Terminal strongly connected components



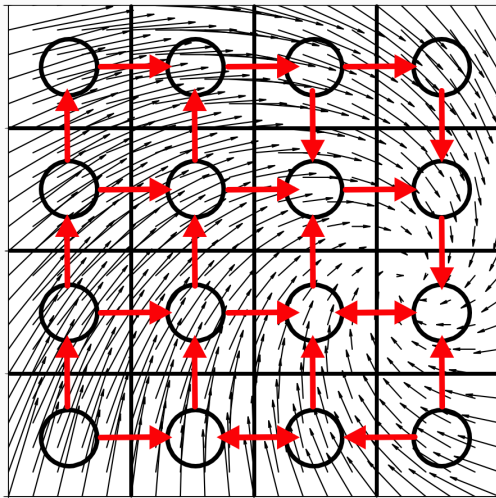
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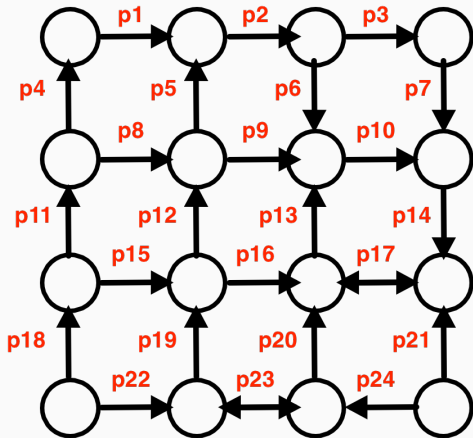
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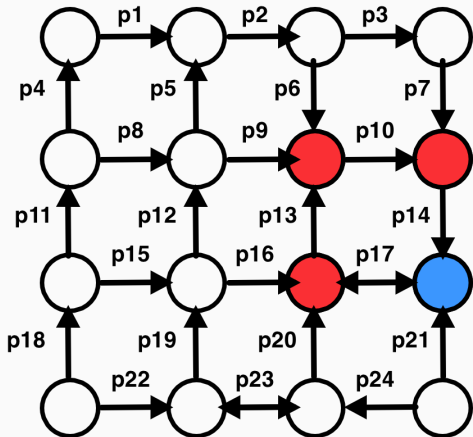
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1. Continuous system \Rightarrow discrete transition system
2. Parameter uncertainty is captured by parametrised edges
3. Parallel parametrised divide and conquer algorithm for component detection
4. Each terminal component over-approximates an attractor

Clark et al. 2014

- Fluxes of inorganic carbon from cytosol to carboxysome
- Fixation using carbonic anhydrase and *RuBisCO* enzyme

Grimaud et al. 2014

- Time-dependent dynamics of nitrogen fixation
- Respecting the obligate nitrogen fixation and light limitation

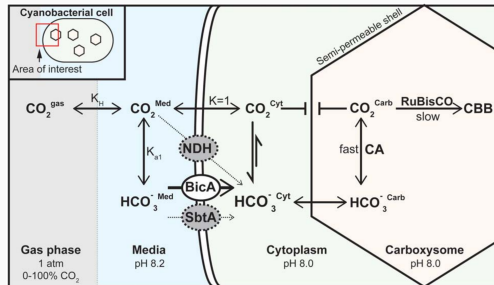
Müller et al. (in devel.)

- Carbon fluxes in a laboratory scale photobioreactor
- Intercellular exchange, carbonate chemistry, and gas-to-liquid CO_2 transfer

Plyusnina et al. (in devel.)

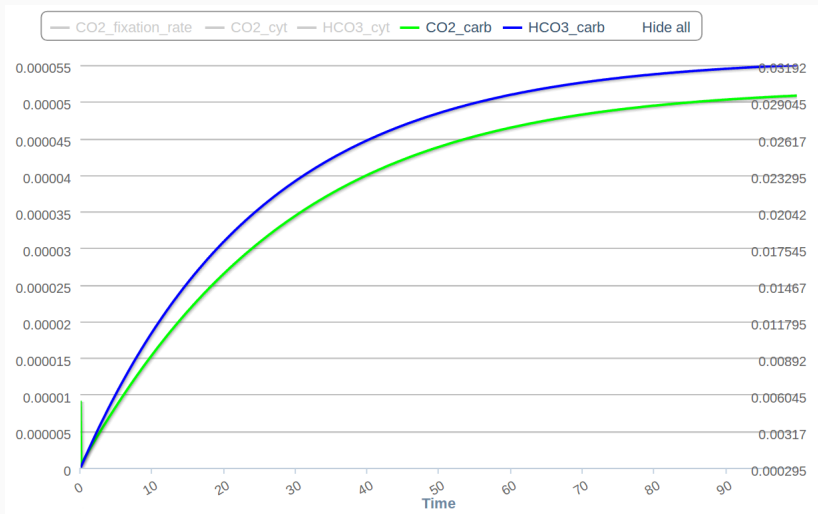
- Electron transport on thylakoid membrane (photosynthesis)

- Fluxes and fixation of inorganic carbon
- Carbon dioxide concentrating mechanism (CCM)
- Model shows that CCM is not necessary for growth in media in equilibrium with concentration of 10% CO_2
- Activity of carbon-fixing enzyme *RuBisCO*
- Parameter *fast* affects rate of carbon fixation reaction



¹Ryan L. Clark et al., Insights into the industrial growth of cyanobacteria from a model of the carbon-concentrating mechanism, *AIChE Journal*, 2014, <https://doi.org/10.1002/aic.14310>

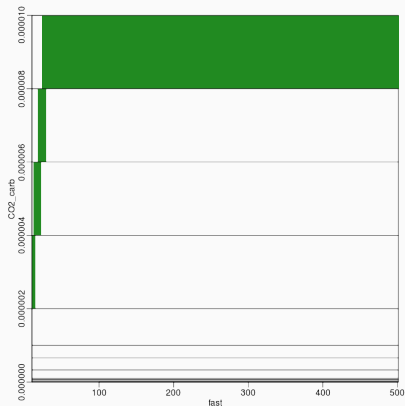
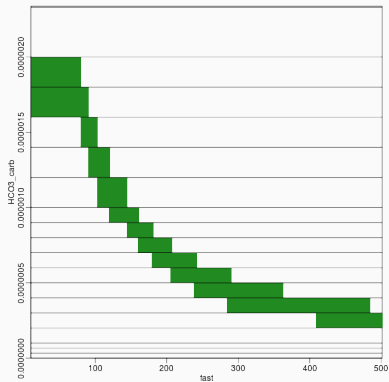
Clark et al. – simulation



Parameter *fast* = 100

A single attractor across whole parameter range

CO_2 increases rapidly with *fast*, HCO_3 decreases for higher values



- Clark: Strong dependence on parameter *fast*, 4 dimensions
- Grimaud: Independent on parameters r_2 and r_4 , 4 dimensions
- Müller: Independent on parameter $kLA_{CO_2_eff}$, 7 dimensions
- Plyusnina: 8 dimensions, strange non-trivial attractor

<http://pithya.ics.muni.cz/app/pithya>

PITHYA: Parameter Investigation Tool



Select predefined example

Advanced

[Click here for tutorial](#) or [here for complete manual](#) or [watch video slides on YouTube](#)

Select example

Settings

Editor

Explorer

Results

Model Editor Control Panel

Browse...

✕ Reload Model

Generate Approximation

Upload complete

Save Model

Properties Editor Control Panel

Browse...

✕ Reload Properties

Run Parameter Synthesis

Save Properties

Run Attractor Analysis

Analyses Control Panel

Model Editor

Properties Editor

```
1 VARS: CO2_cyt, HCO3_cyt, CO2_carb, HCO3_carb
2
3 # Notes:
4 # K4_fact means  $K_4 \cdot (1 + O_2\_carb / K_5)$ 
5 # pH_carb_factor means  $k_4 / 10^{(-pH\_carb)}$ 
6 # pH_cyt_factor means  $k_4 / 10^{(-pH\_cyt)}$ 
7 CONSTS: k2,27128; k3,0.00004; factorCO2dehyd,1; factorHCO3dehyd,1; v2,0.0149764706; K4_fact,0
8 PARAMS: pH_cyt_factor,0.00000001,0.00001; fast,0.20000
9
10 Eq: CO2_cyt = fast*(0.0229086765*0.0004*CO2_cyt) - k2*CO2_cyt*pH_cyt_factor + k3*HCO3_cyt
11 Eq: HCO3_cyt = k2*CO2_cyt*pH_cyt_factor - k3*HCO3_cyt + 0.0026181698 - fast*HCO3_cyt + fast*H
12 Eq: CO2_carb = factorHCO3dehyd*fast*k3*HCO3_carb - factorCO2dehyd*fast*k2*pH_carb_factor*CO2
13 Eq: HCO3_carb = factorCO2dehyd*fast*k2*pH_carb_factor*CO2_carb - factorHCO3dehyd*fast*k3*HCO3
14
15 VAR_POINTS: CO2_carb:1500,10
16
17 THRES: CO2_cyt: 0, 0.00000019, 0.00000039, 0.00000078, 0.00000156, 0.000003125, 0.00000625,
18 THRES: HCO3_cyt: 0, 0.00019, 0.00039, 0.00078, 0.00156, 0.003125, 0.00625, 0.0125, 0.025, 0.0
19 THRES: CO2_carb: 0, 0.001
20 THRES: HCO3_carb:0, 0.00019, 0.00039, 0.00078, 0.00156, 0.003125, 0.00625, 0.0125, 0.025, 0.0
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Software support: Pithya

<http://pithya.ics.muni.cz/app/pithya>

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Properties Editor

1

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Thank you for your attention!