# Cellular decision making models in yeast

ALDO ESTEFANO ENCARNACIÓN SEGURA

Cellular decision making

- Expressed phenotype

  ◦ Foraging
  ◦ Cell differentiation
  ◦ Apoptosis

- *Saccharomyces cerevisiae* sugar consumption dynamics
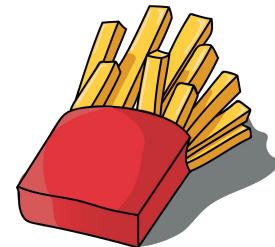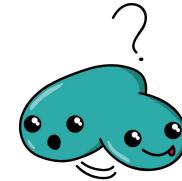
Model

- Symmetric, non-specific

- Fit to experimental data

  ◦ Single sugar
  ◦ Mixture

- Bifurcation
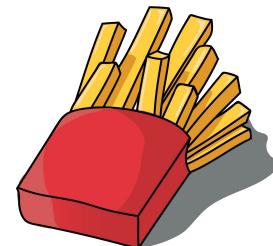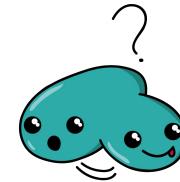
Model

B $\rightarrow$ biomass

G $\rightarrow$ global inhibition signal

P_i $\rightarrow$ metabolic activity

S_i $\rightarrow$ intracellular sugar concentration

N_i $\rightarrow$ extracellular sugar concentration
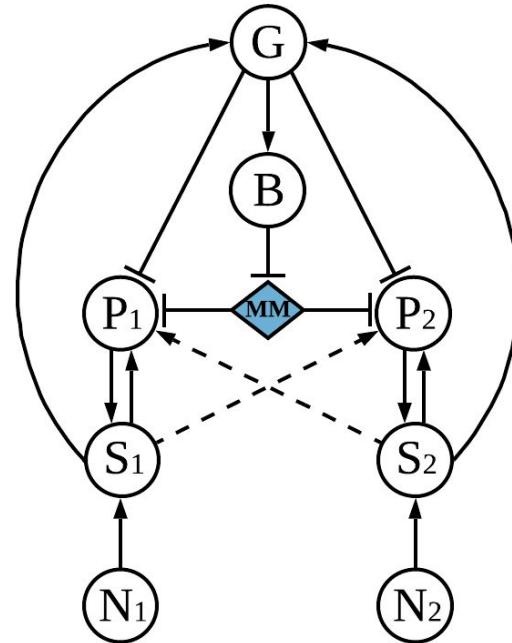
Model

$$\frac{dB}{dt} = V_B \frac{G^2}{K_G^2 + G^2} - Dcy_B \ B$$

$$\frac{dG}{dt} = Y_1 \ V_{G_1} \ S_1 + Y_2 \ V_{G_2} \ S_2 - V_B \ G \ \frac{G^2}{K_G^2 + G^2}$$

$$\frac{dN_i}{dt} = -V_{S_i} \ P_i \ \frac{N_i^2}{K_{S_i}^2 + N_i^2}$$

$$\frac{dS_i}{dt} = V_{S_i} \ P_i \ \frac{N_i^2}{K_{S_i}^2 + N_i^2} - V_{G_i} S_i$$

$$\frac{dP_i}{dt} = V_{P_i} \ Base_{P_i} - Dcy_{P_i} \ P_i + V_{P_i} \left((MM \ B) - P_1 - P_2 \right)$$

$$\frac{(S_1 + S_2 \ K_{SI_1})^2}{(S_1 + S_2 \ K_{SI_1})^2 + (K_{P_i} \ (1 + \frac{G}{K_{inh_1}}))^2}$$
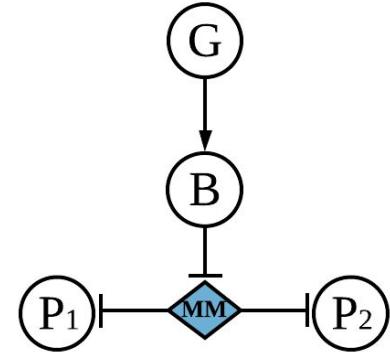
Experimental data

- Mal12 marked with mCherry
- Gal10 marked with GFP
- Optical density (OD)

| Experiment	Maltose	Galactose
Single sugar	0.25 - 4%	-
Single sugar	-	0.125 - 2%
Sugar mixture	0.25 - 1%	0.125 - 0.5%

Experimental data

- Maltose
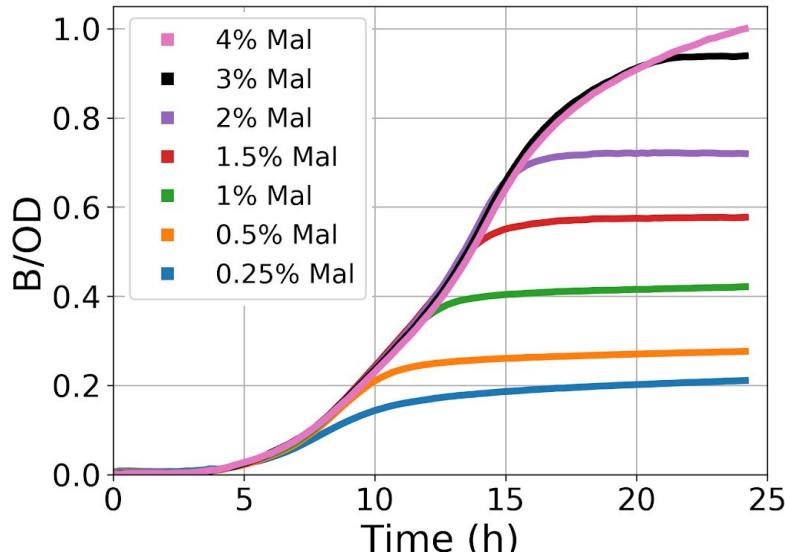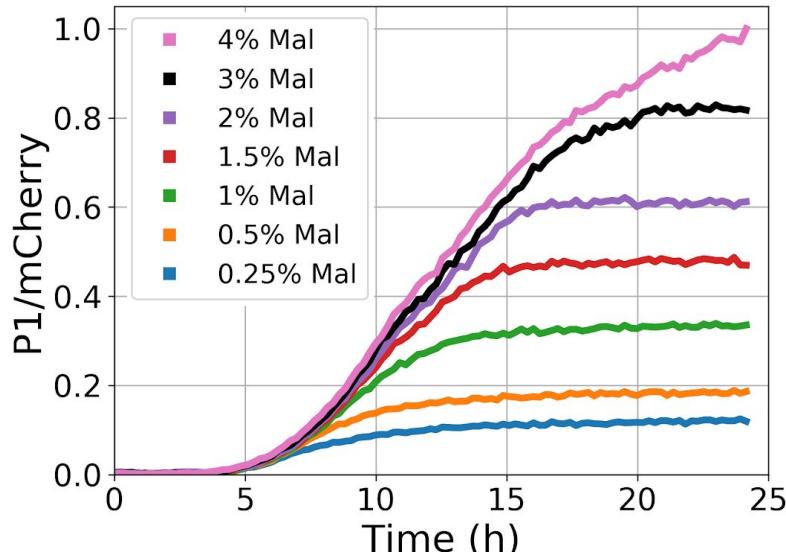
# Experimental data

- Sulfur mixture
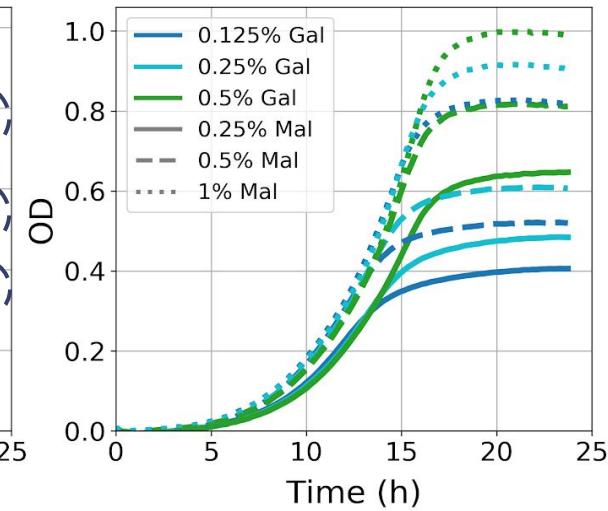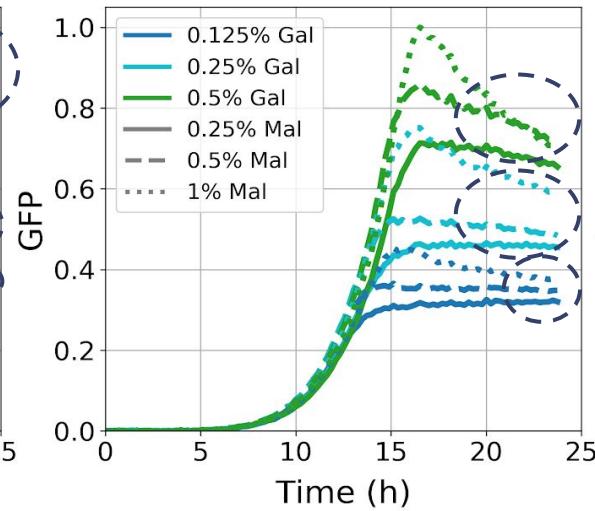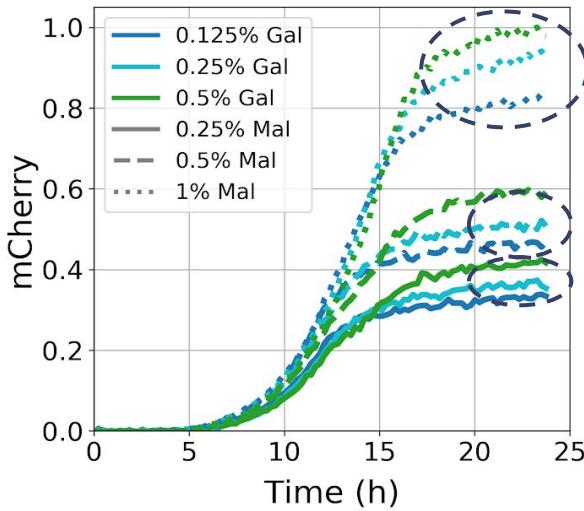
Parameterisation

- Parameter values from literature

- Optimisation routine
  - Normalise data and model output
  - Algorithm: scipy.optimize.minimize(method='L-BFGS-B')
  - Objective function: weighted RMSE

$$RMSE = \sqrt{\sum_{j=1}^{c} \frac{\sum_{i=1}^{m} w_{ji}(\hat{x}_{ji} - x_{ji})^2}{c}}$$

Maltose fitting

- RMSE: 0.06358
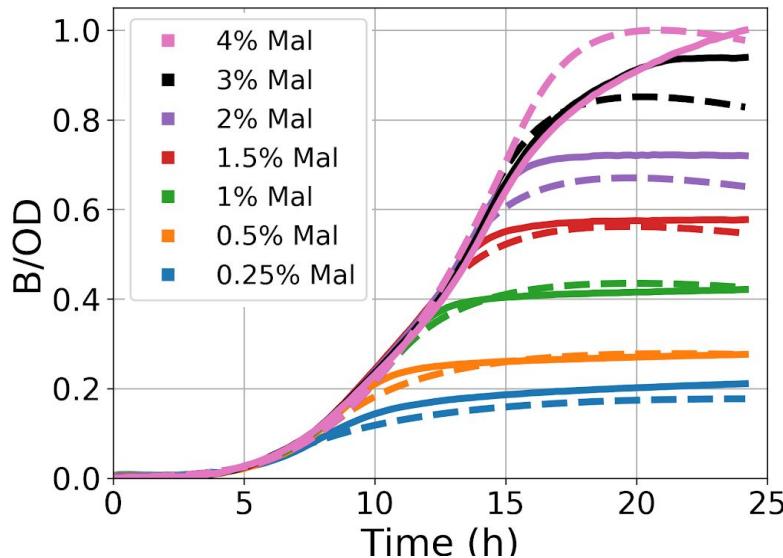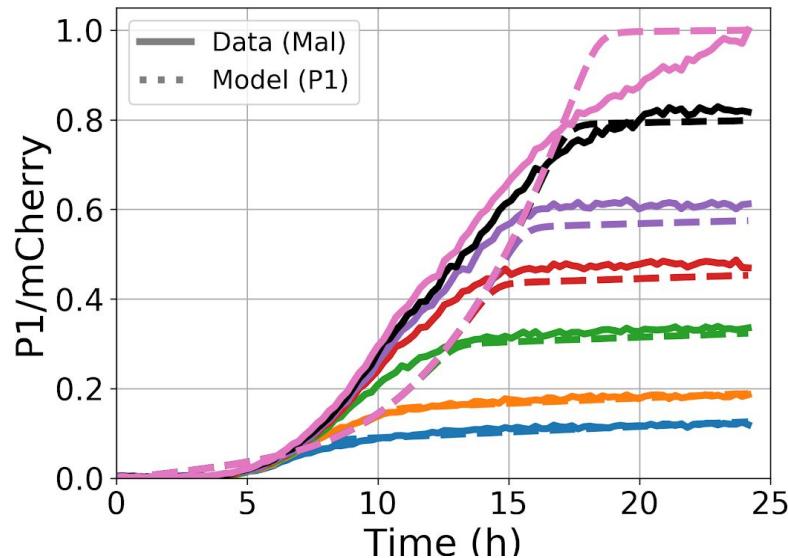
Galactose fitting

- RMSE: 0.05158
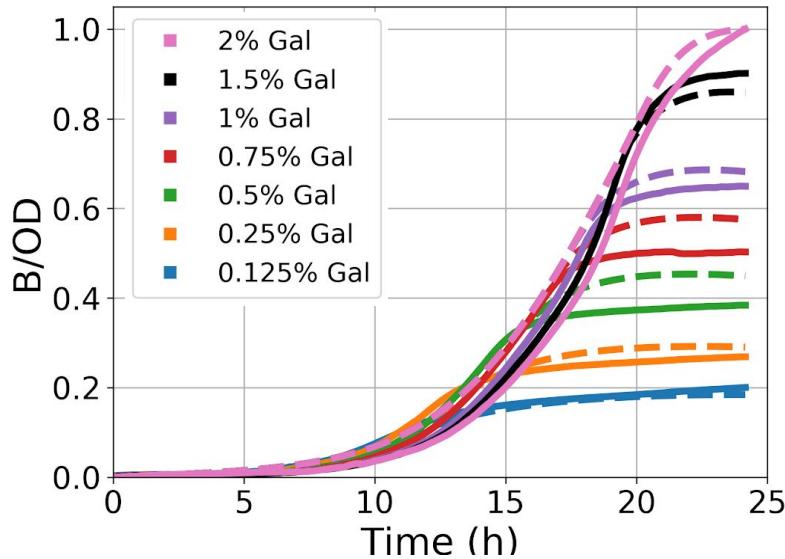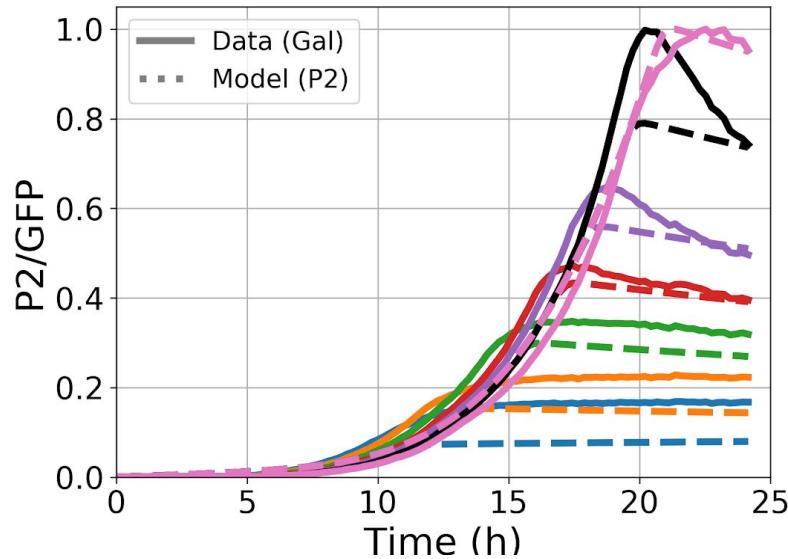
- Sugar mixture fitting PR1

- RMSE: 0.06591
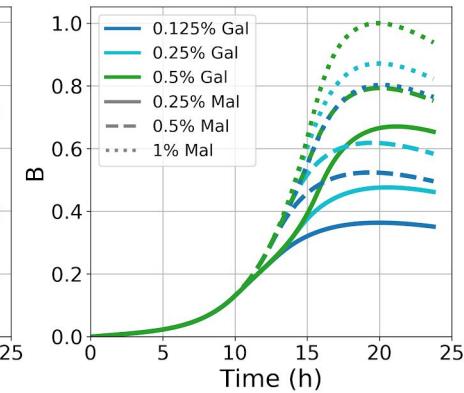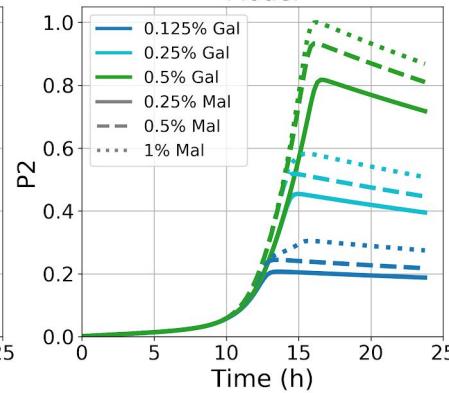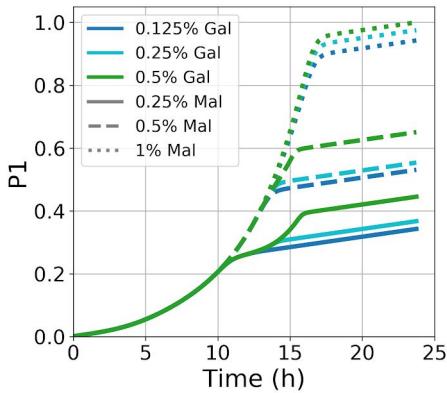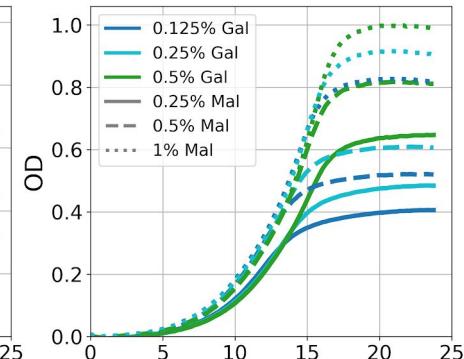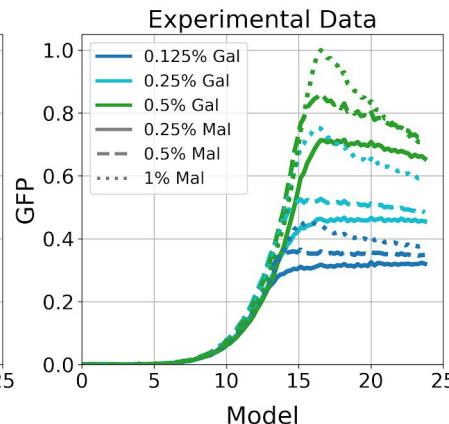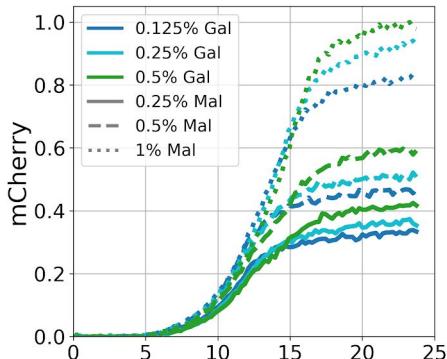
Single parameter set

- 3 different parameter sets

- PR1 optimised parameters
  - Modified the DcyB
 - Changed initial conditions

- Maltose

  - Exclusive maltose fit
    - RMSE: 0.0635
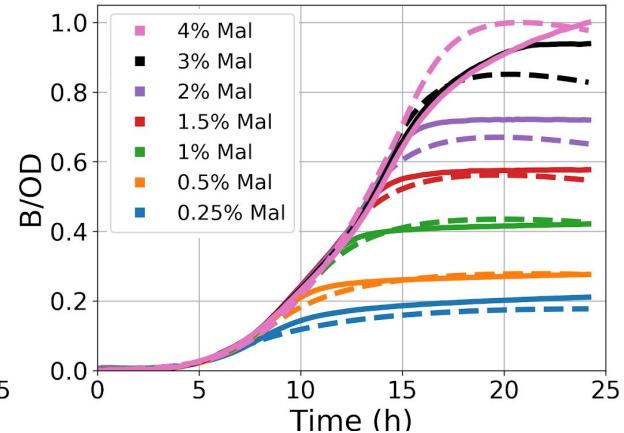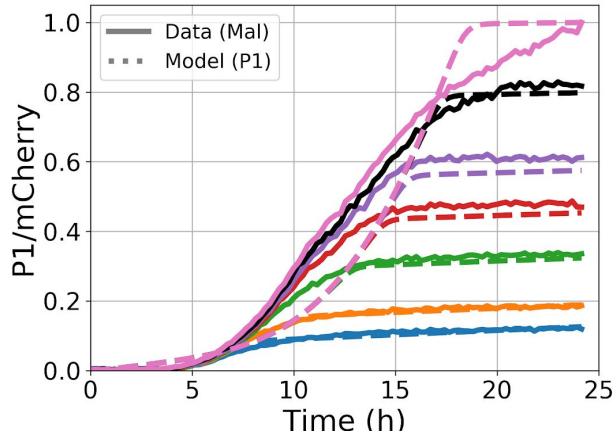
 - Modified PR1 parameters
   - RMSE: 0.06764
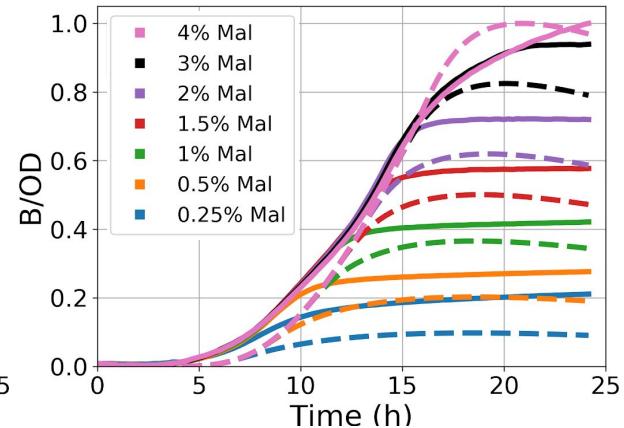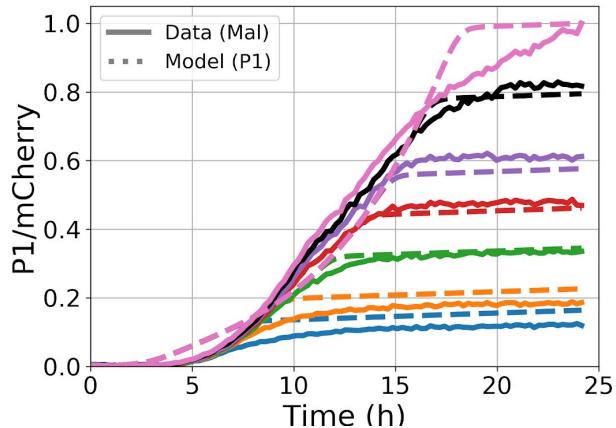
- Galactose

  - Exclusive galactose fit
    - RMSE: 0.05158
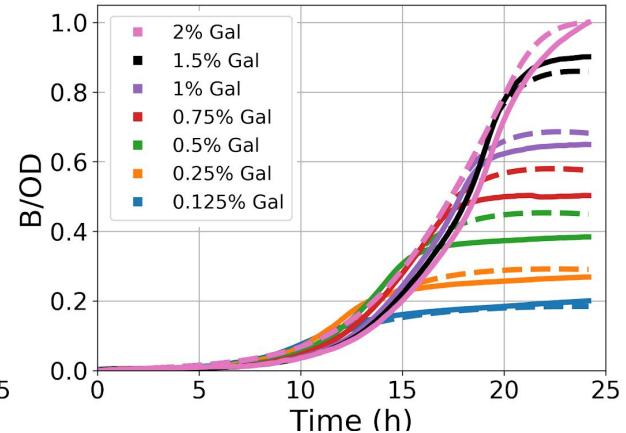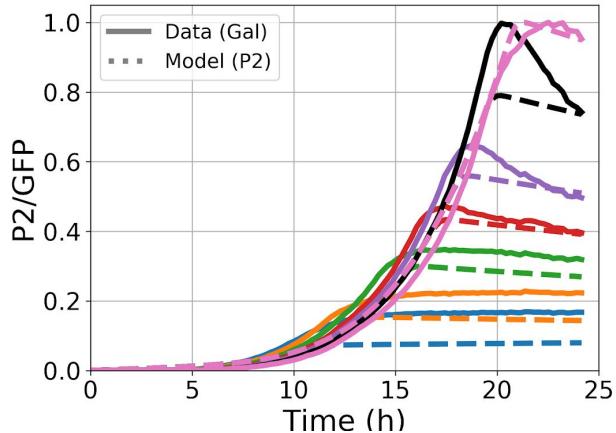
- Modified PR1 parameters
  - RMSE: 0.06906
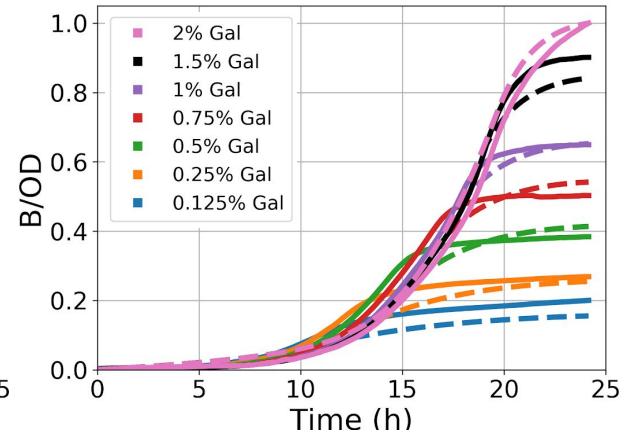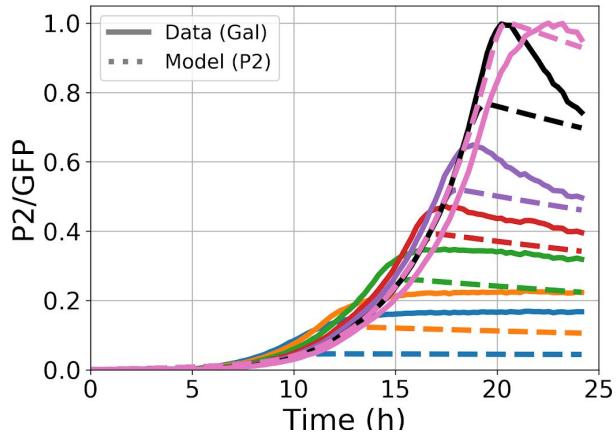
- PR1

- Exclusive PR1 fit
 - RMSE: 0.06591

- Modified PR1 parameters
 - RMSE: 0.06644
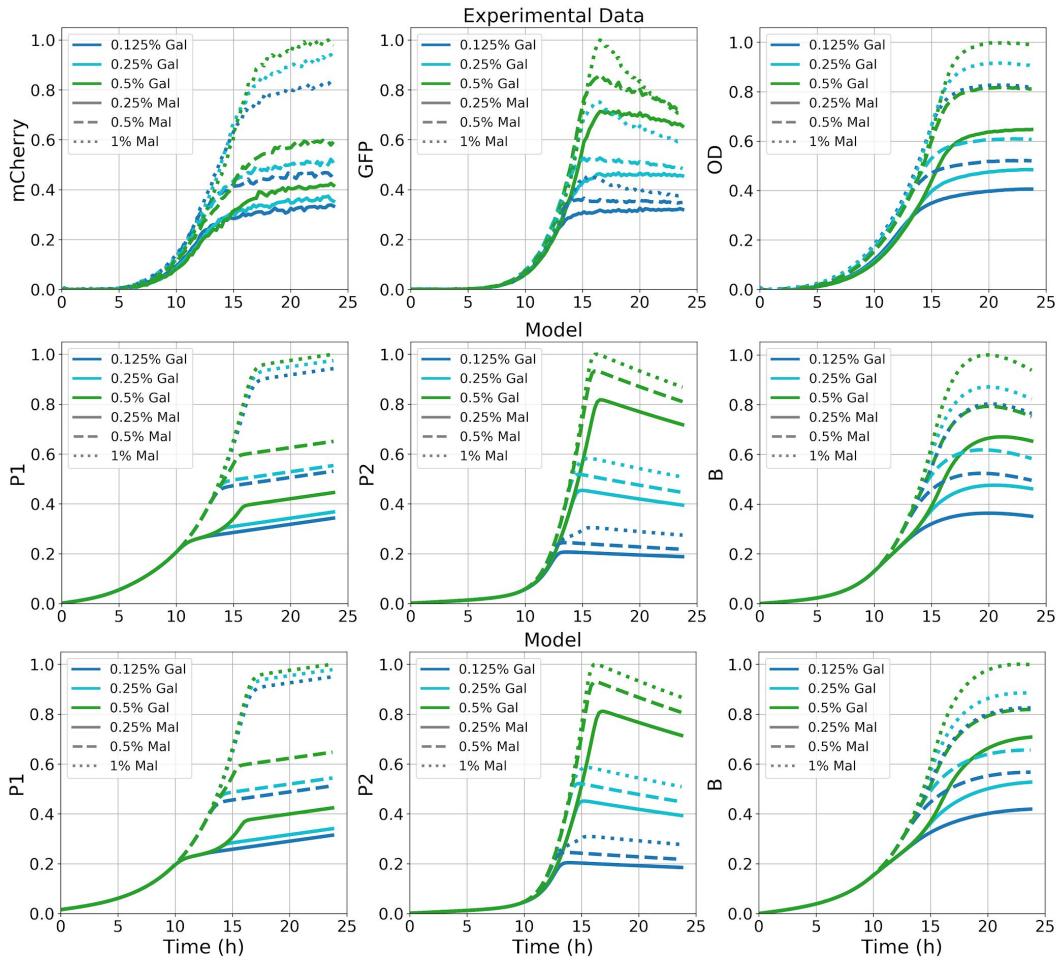
Bifurcation analysis

- Equal value alternatives
  - Same parameters (Galactose)

    - Quality/affinity $\propto 1/K_p$
    - Inhibition strength $\propto 1/K_{inh}$

- Steady state conditions for Ni
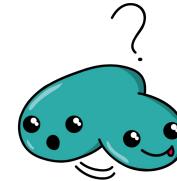
Bifurcation analysis

- Inhibition strength ∝ $1/K_{inh}$
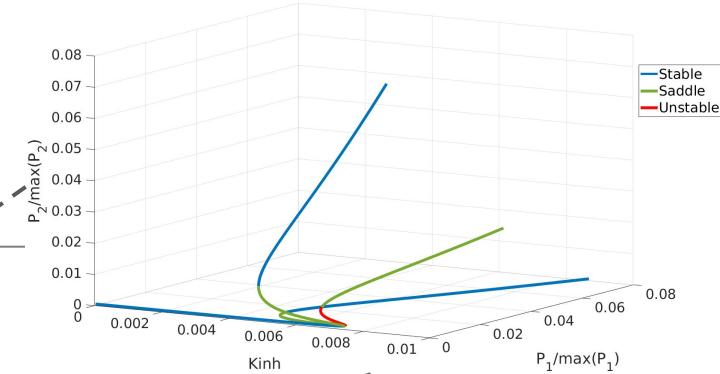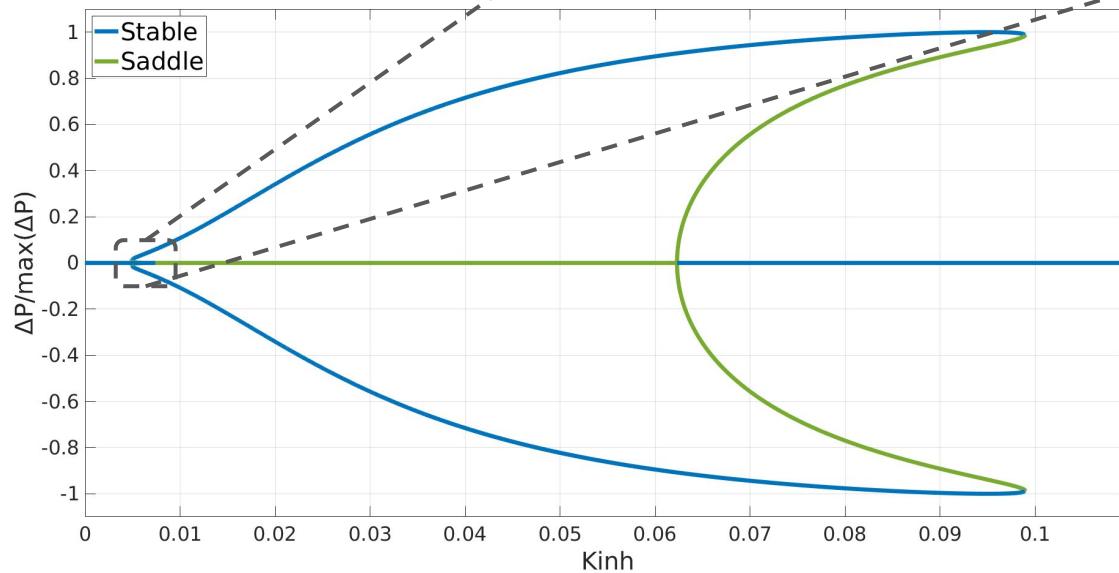
Bifurcation analysis

- Quality/affinity $\propto 1/K_P$
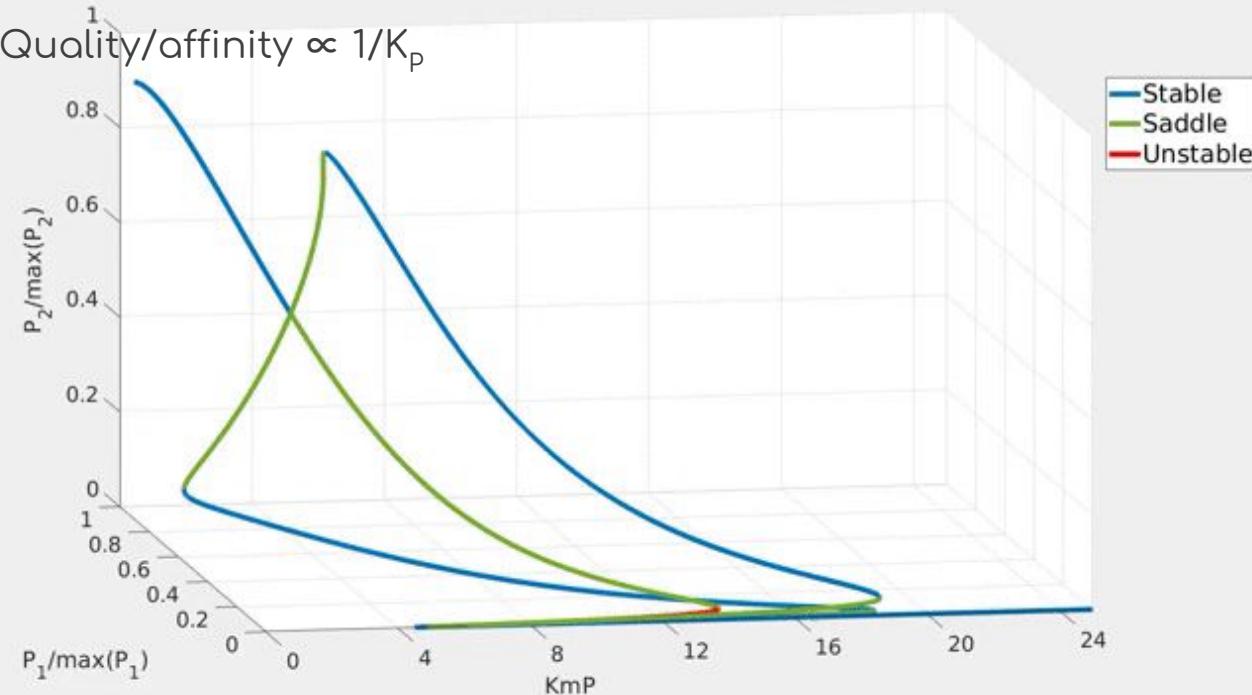
Bifurcation analysis

- Quality/affinity $\propto 1/K_p$

  - Data fitting K_p range: 0.01 ~ 0.08
  - Bifurcation K_p range: 3.5 ~ 19

    ◦ Bifurcation K_p conditions: Low affinity, Low inhibition

- Inhibition strength $\propto 1/K_{inh}$

  - Data fitting K_{inh} range: 2.6 ~ 3.6
  - Bifurcation K_{inh} range: 0.005 ~ 0.1

    ◦ Bifurcation K_{inh} conditions: High affinity, High inhibition

Conclusions

- A relatively simple DM model can reproduce experimental data for several sugar concentrations and different experimental conditions

- The model presents the dynamical behaviour required to better explore the decision making dynamics of the system

Questions