

## Enzyme rhythms in model `glycogen_storage_dilution.speedy` - enzymes are activated

Model name: `glycogen_storage_dilution`

### o Optimisation problem

- Protein turnover time  $1 \text{ s} = 0.0167 \text{ min}$
- Perturbed parameter(s) : `x1`
- Perturbation frequency  $f$  :  $0.05/\text{s}$  (period 20 s)
- Scored quantity: `glucose`
- Scored quantity: `v4`
- Fitness-averaged fitness
- No posttranslational rhythms allowed
- Standard frequency considered  $f$  :  $0.05/\text{s}$  (period 20 s)

### o Model properties:

- `inactive_enzymes`: 1
- `balanced_reference_state`: 0
- `consider_external_rhythm`: 1
- `adaptive_rhythm`: 1
- `spontaneous_rhythm`: 0
- `spontaneous_rhythm_at_omega`: 0
- `has_spontaneous_rhythm_and_inactive_enzymes`: 0

### o No beneficial autonomous oscillation found

### o Fitness changes after external perturbation at frequency $f=0.05/\text{s}$

- Change by perturbation alone (`xx`): -17.9
  - Change by adaption synergies (`xu`): 35.5
  - Change by periodic enzyme (`uu`): -17.7
  - Change by enzyme mean shift (`u`): -0.0429
  - Total fitness change : -0.127
  - Fitness gain by adaption : 17.7
  - Maximum adaptive fitness found (in tested range) at frequency  $f = 0.224/\text{s}$  (period 4.47 s)
  - Predicted max. fitness change (adaptive, num. opt, full ampl. constraints) at frequency  $f = 0.224$ : 0.0609
- Inactive enzymes found; computing adaptive rhythms with shifted mean values in 1st order approximation

### o Autonomous oscillations?

### o Numerical calculation (responsive, $f=0.05$ )

- Fitness change (fitness-averaged): -17.9
- Fitness change (state-averaged):  $-8.53e-05$

### o Numerical calculation (adaptive, $f=0.05$ )

- Fitness change (fitness-averaged): -0.469
- Fitness change (state-averaged): -0.357

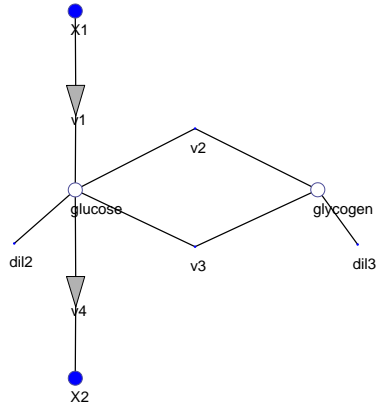


Figure 1: Network and reference flux

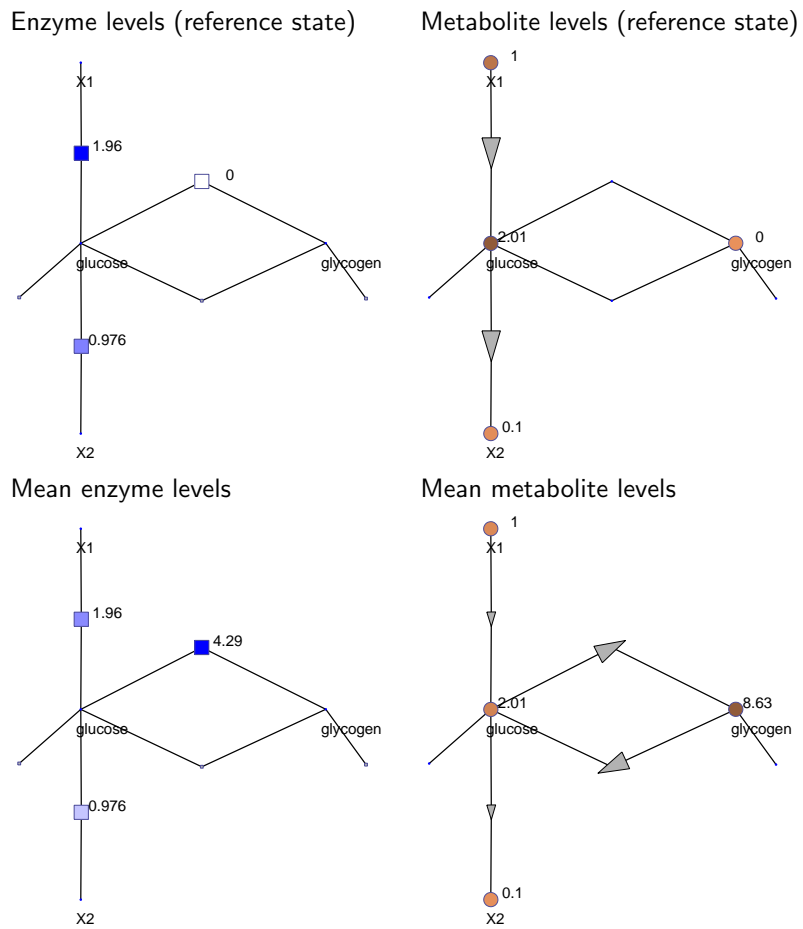
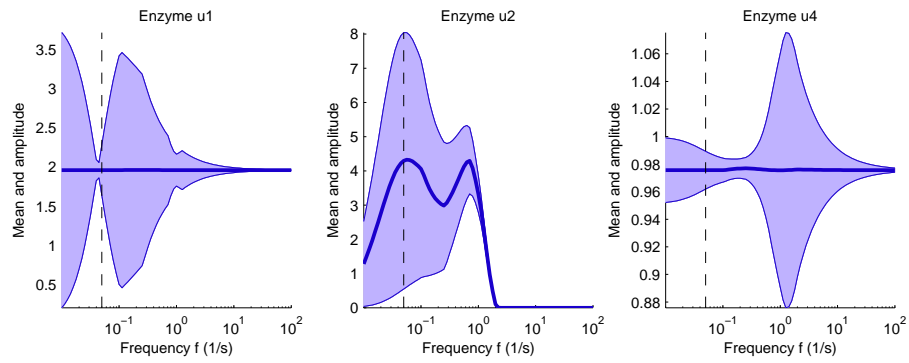
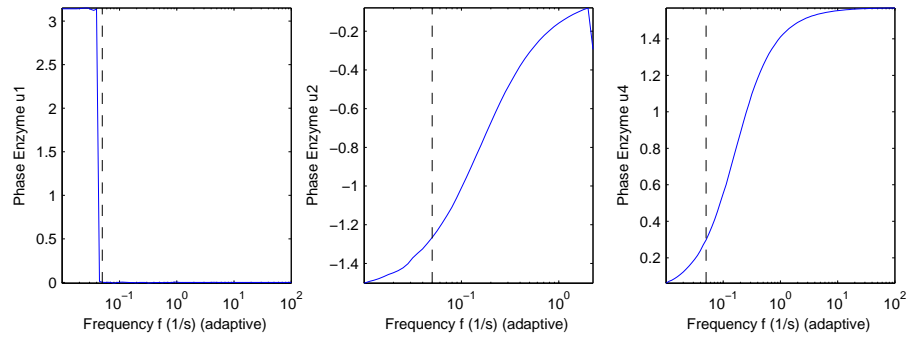


Figure 2: Reference state (top) and mean state during oscillation (bottom).

Protein level and enzyme activity (mean and amplitude)



Phase angles  $[0, 2\pi]$



Fitness change

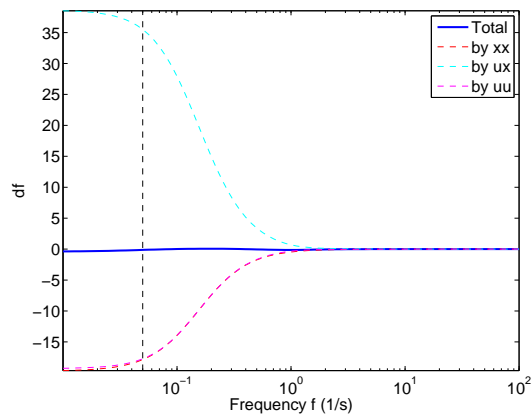


Figure 3: Adaptive oscillations. Left: amplitudes of protein levels (blue) and modification (grey). Right: phase shifts.

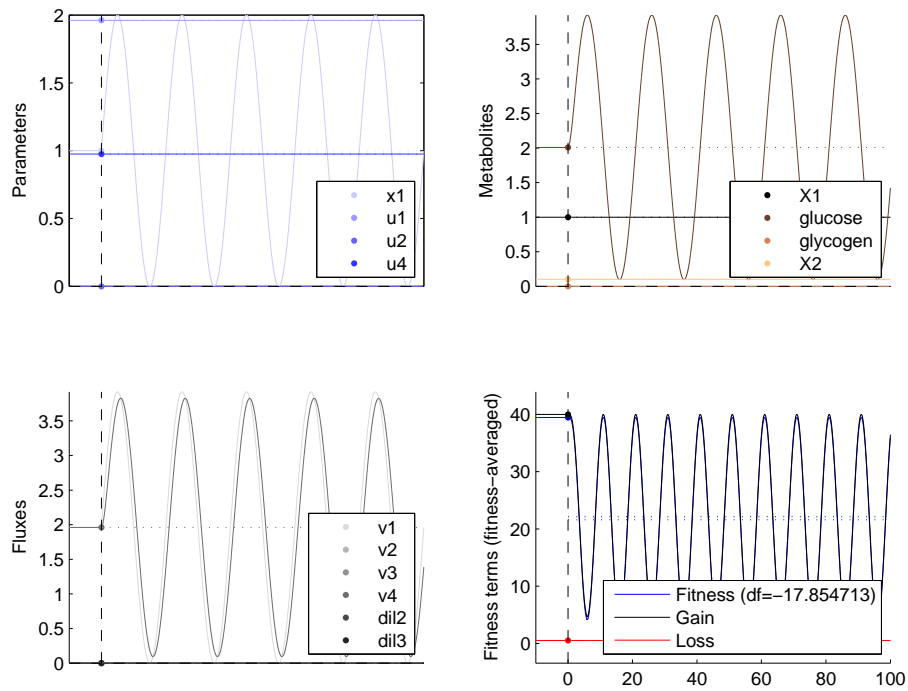


Figure 4: Numerical calculations: responsive oscillations (curves). Dynamic effects of oscillations. The panels show different types of variables: (i) Optimal periodic enzyme levels; (ii) internal metabolite levels; (iii) reaction fluxes; (iv) fitness, benefit, and cost.

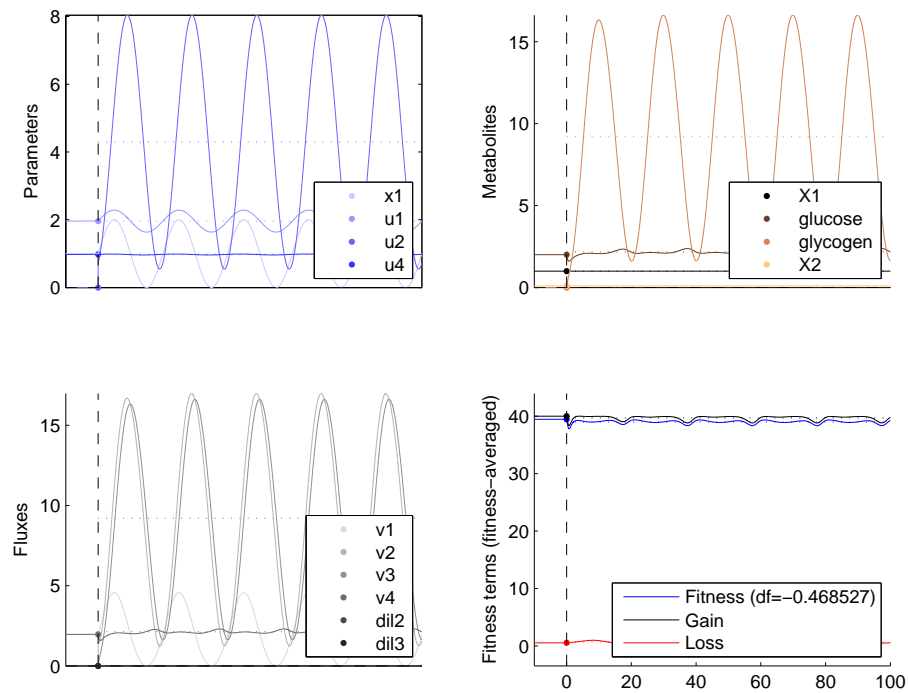
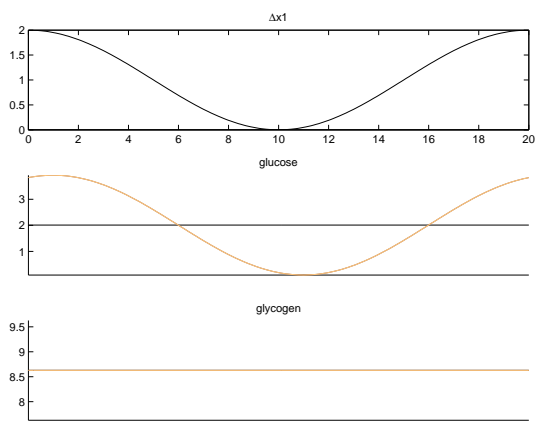
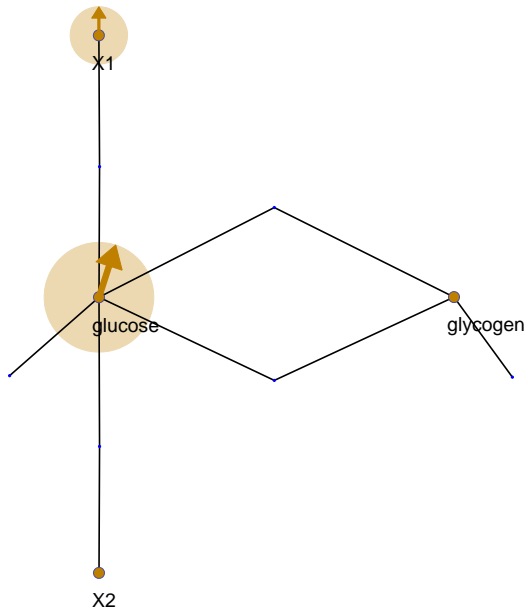


Figure 5: Numerical calculations: adaptive oscillations (curves). Dynamic effects of oscillations. The panels show different types of variables: (i) Optimal periodic enzyme levels; (ii) internal metabolite levels; (iii) reaction fluxes; (iv) fitness, benefit, and cost.

Responsive oscillations (concentrations)



Responsive oscillations (fluxes)

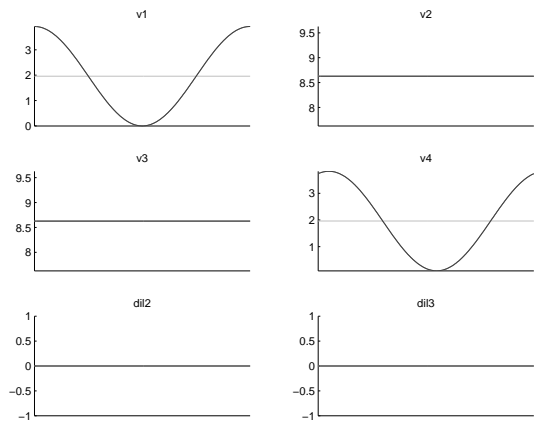
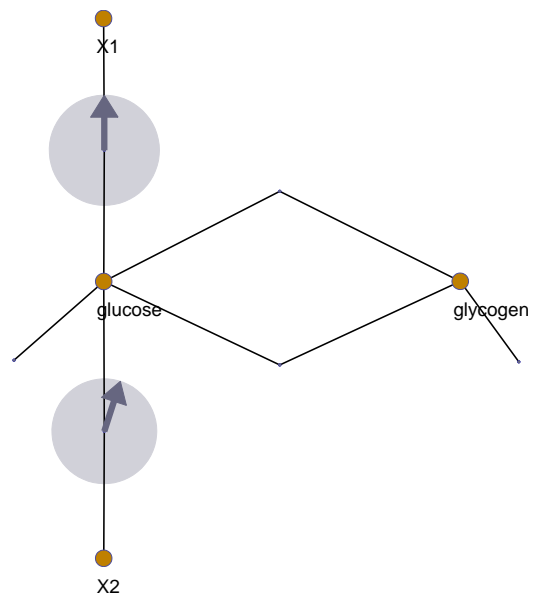
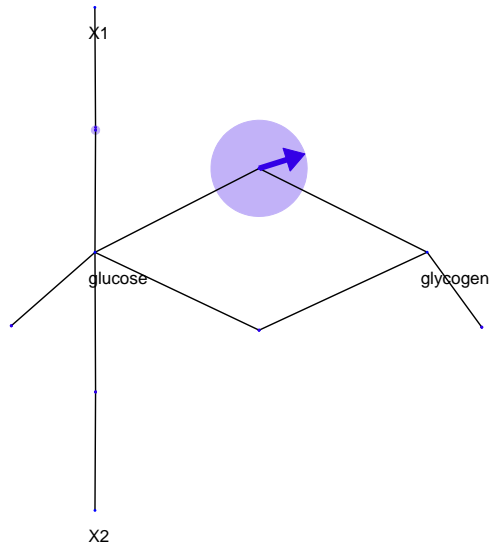
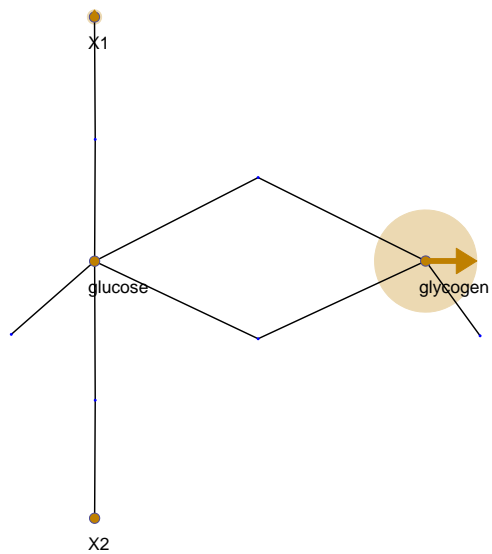


Figure 6: Responsive oscillations (local expansion; arrows: absolute changes)

### Adaptive oscillations (enzymes)



### Adaptive oscillations (metabolites)



### Adaptive oscillations (fluxes)

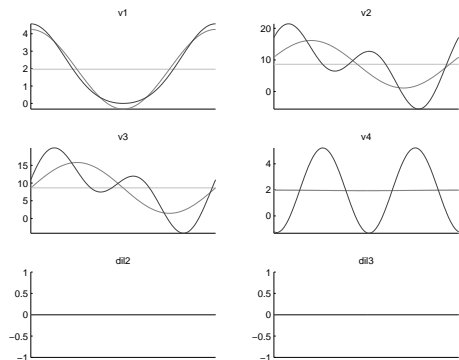
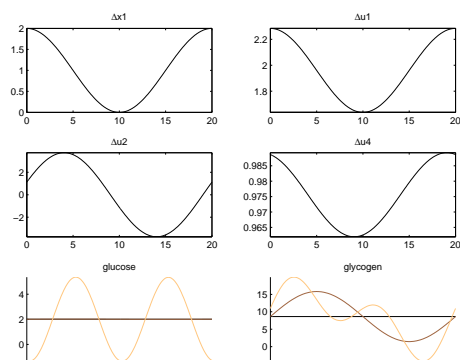
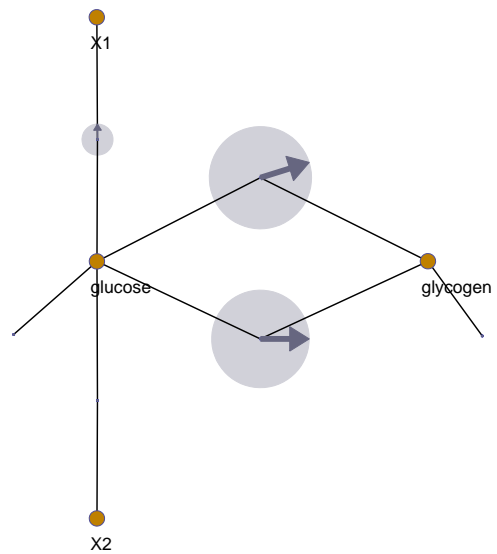


Figure 7: Adaption to forced oscillations (local expansion; arrows: absolute changes)

Adaptive

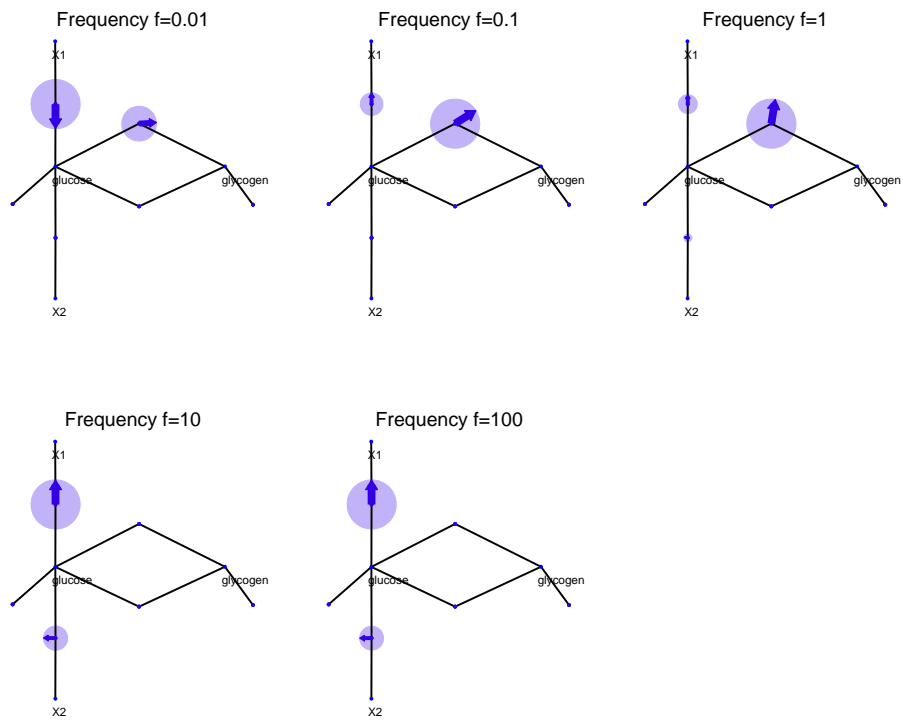
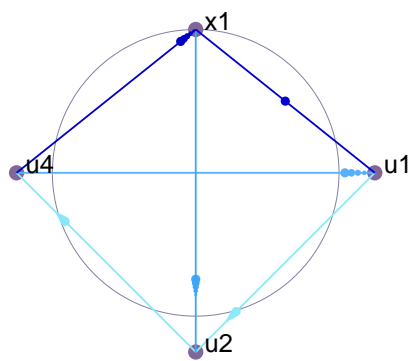
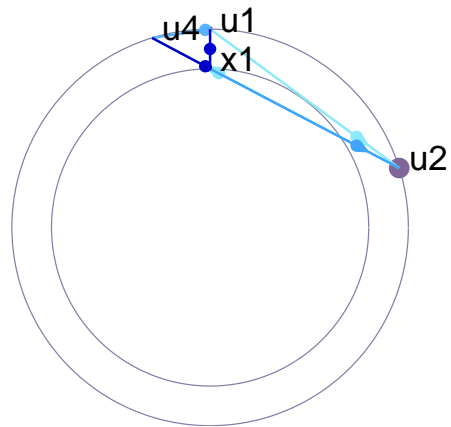


Figure 8: Adaptive oscillations for several frequencies (from local expansion).

Synergies



Synergy phase plot



Synergies on network

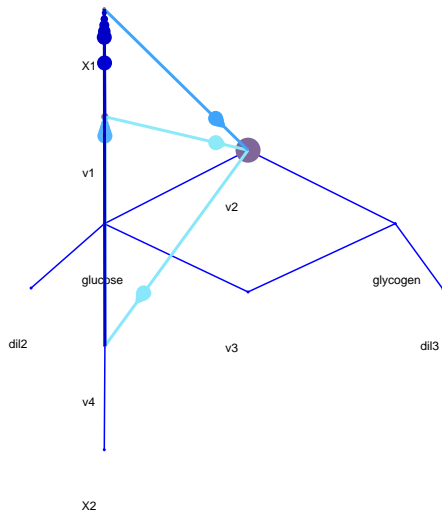


Figure 9: Periodic economic potentials and direct enzyme values.