

## Enzyme rhythms in model linear\_chain4\_irrev

Model name: linear\_chain4\_irrev

### o Optimisation problem

- Protein turnover time  $1.8e+03$  s = 30 min
- Perturbed parameter(s) : x1
- Perturbation frequency  $f$  : 1/s (period 1 s)
- Scored quantity: v4
- Fitness-averaged fitness
- Posttranslational rhythms allowed
- Standard frequency considered  $f$  : 1/s (period 1 s)

### o Model properties:

- inactive\_enzymes: 0
- balanced\_reference\_state: 1
- 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 self-induced oscillation found

### o Fitness changes after external perturbation at frequency $f=1/s$

- Change by perturbation alone (xx):  $-9.21e-05$
- Change by adaption synergies (xu): 1.99
- Change by periodic enzyme (uu): -1.79
- Change by enzyme mean shift (u):  $-4.75e-08$
- Total fitness change : 0.199
- Fitness gain by adaption : 0.199
- Maximum adaptive fitness found (in tested range) at frequency  $f=0.000158/s$  (period  $6.31e+03$  s)
- Predicted max. fitness change (adaptive, num. opt, full ampl. constraints) at frequency  $f=0.000158$ : 0.876

### o Self-induced oscillations?

- No beneficial self-induced oscillations (2nd order, amplitude below 1/2 of mean) found at frequency  $f = 1/s$  (principal synergy = -0.0154): Predicted fitness change -0.169

### o Numerical calculation (responsive, $f=1$ )

- Fitness change (fitness-averaged):  $-7.15e-05$
- Fitness change (state-averaged):  $2.06e-05$

### o Numerical calculation (adaptive, $f=1$ )

- Fitness change (fitness-averaged): 1.42
- Fitness change (state-averaged): 1.84

### o Numerical calculation (self-induced rhythm, amplitude below 1/2 of mean, $f=1$ )

- Fitness change (fitness-averaged) :  $2.25e-05$
- Fitness change (state-averaged):  $2.25e-05$

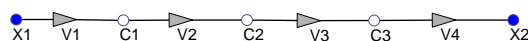


Figure 1: Network and reference flux

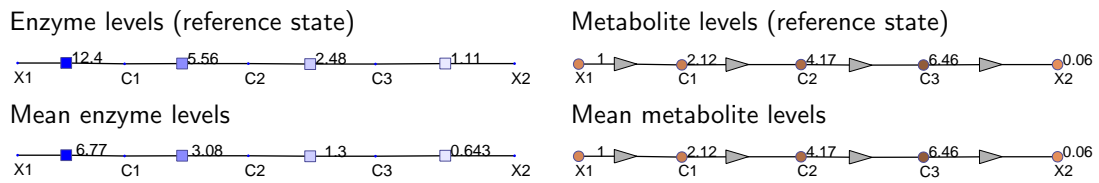


Figure 2: Reference state (top) and mean state during oscillation (bottom).

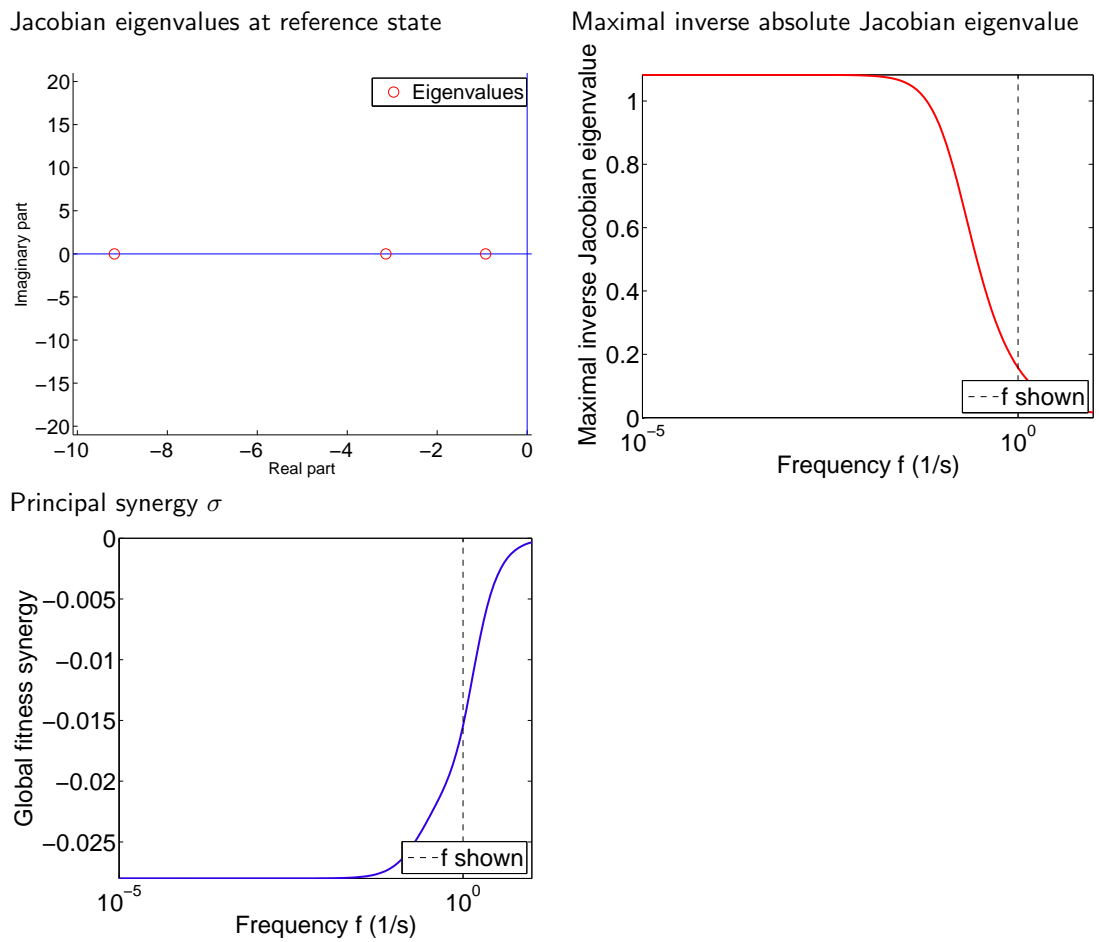
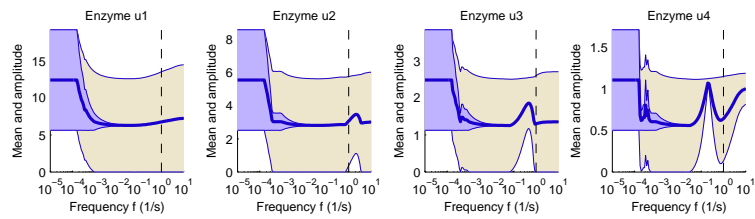
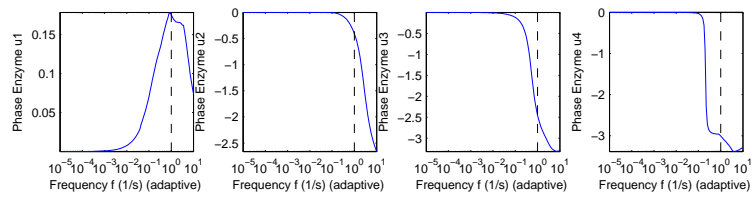


Figure 3: Control analysis. Left: Global fitness synergy (maximal fitness curvature eigenvalue), as a function of the frequency. Right: Relative amplitudes of individual enzymes for the least wasteful enzyme mode (components of the leading fitness curvature eigenvector).

Protein level and enzyme activity (mean and amplitude)



Phase angles  $[0, 2\pi]$



Fitness change

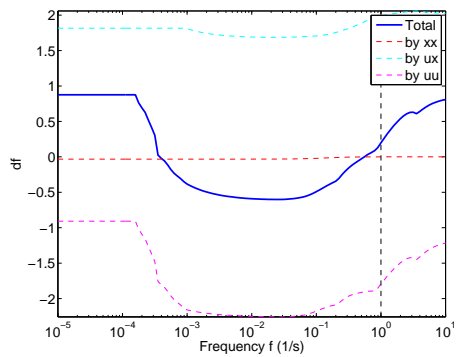


Figure 4: Adaptive oscillations. Left: amplitudes of protein levels (blue) and modification (grey). Right: phase shifts.

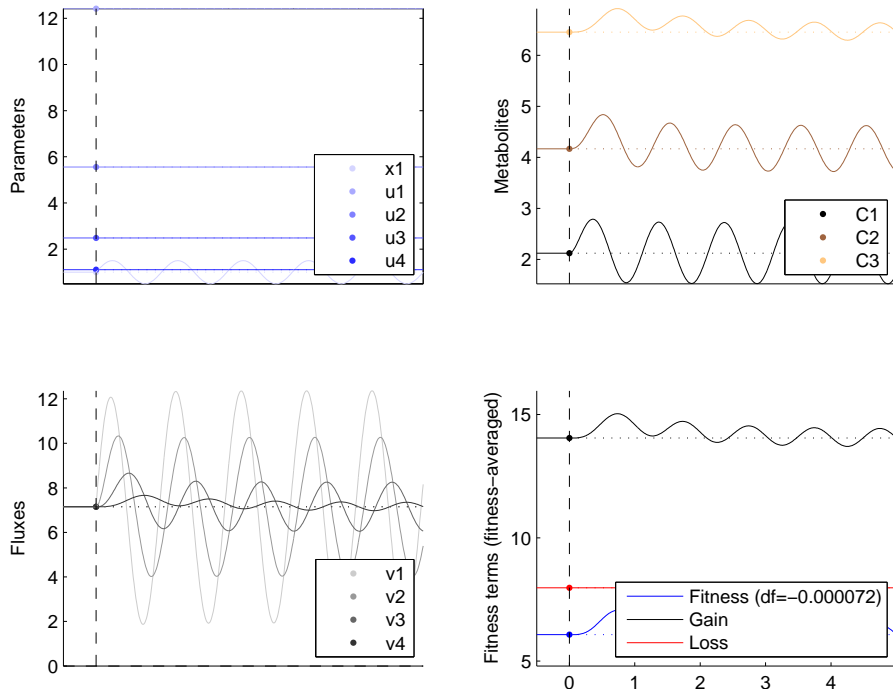


Figure 5: Numerical calculations: responsive oscillations (curves). Dynamic effects of oscillations. The panels show different types of variables: (i) Optimal periodic enzyme levels; (ii) internal metabolite levels; (iii) reaction fluxes; (iv) fitness, benefit, and cost. Perturbation frequency see first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

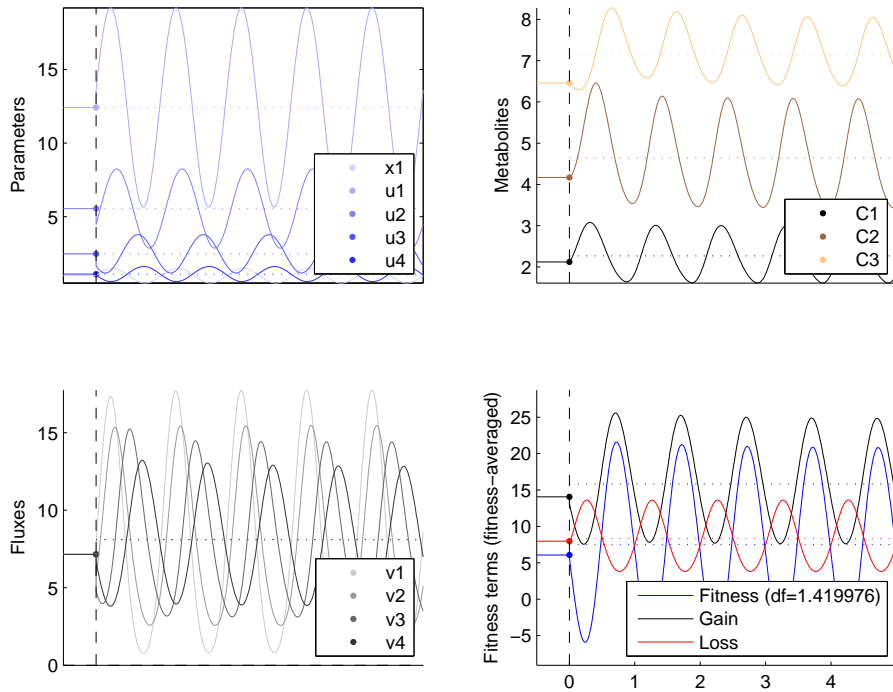


Figure 6: Numerical calculations: adaptive oscillations (curves). Dynamic effects of oscillations. The panels show different types of variables: (i) Optimal periodic enzyme levels; (ii) internal metabolite levels; (iii) reaction fluxes; (iv) fitness, benefit, and cost. Perturbation frequency see first page.

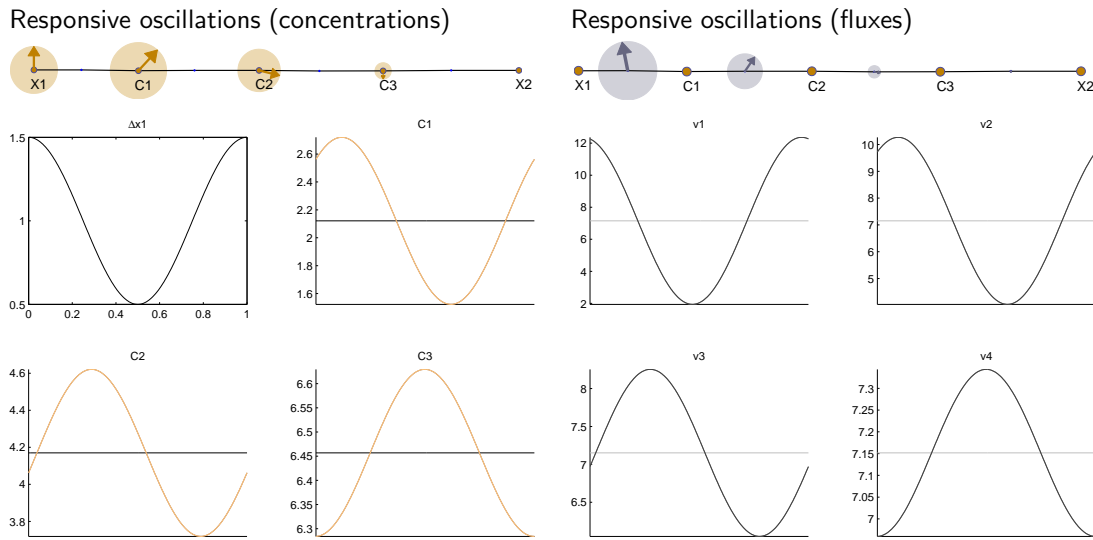


Figure 7: Responsive oscillations (local expansion; arrows: absolute changes) Perturbation frequency see first page.

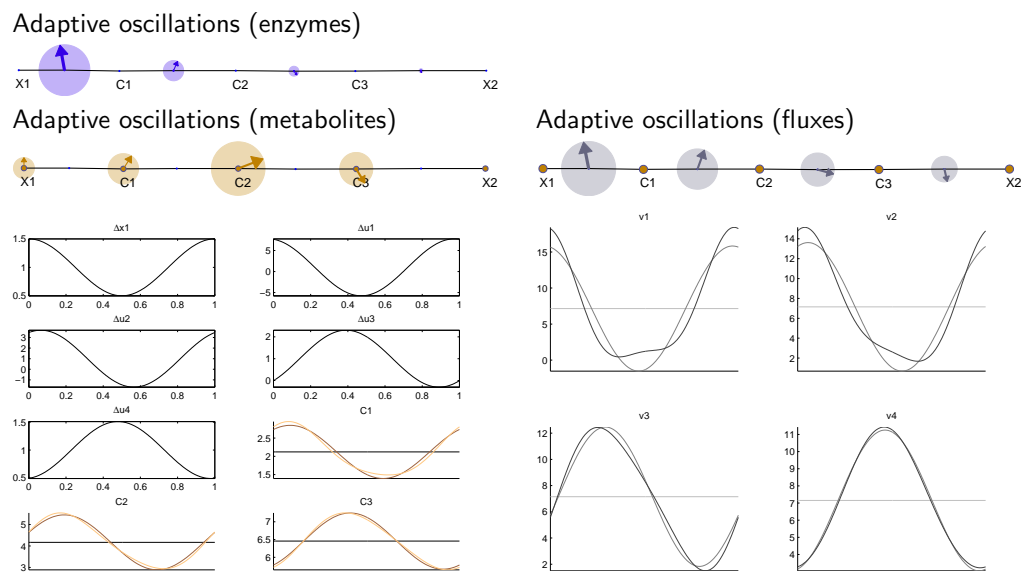


Figure 8: Adaption to forced oscillations (local expansion; arrows: absolute changes). Perturbation frequency see first page.

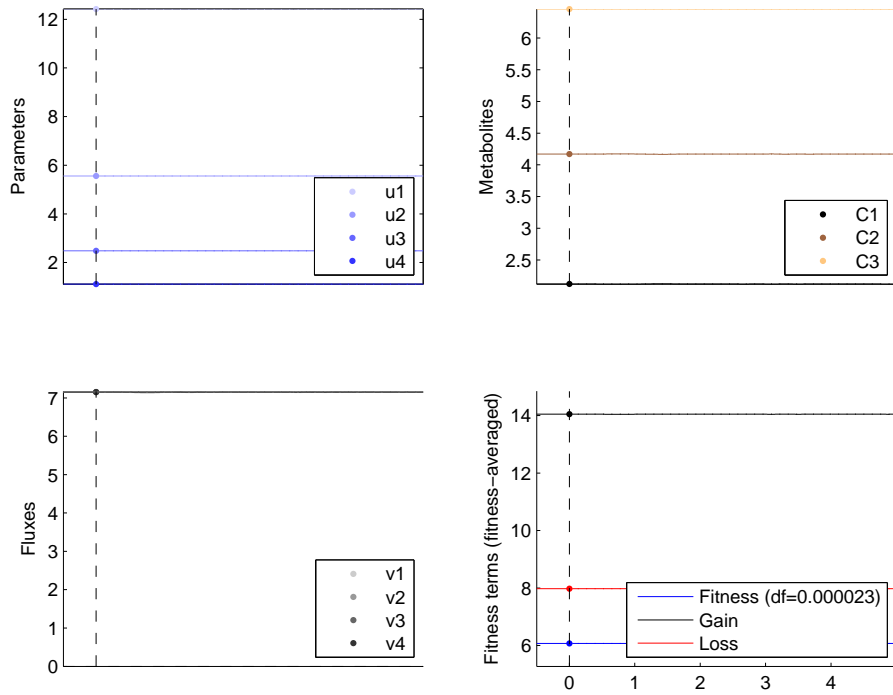


Figure 9: Tentative spontaneous oscillations. Perturbation frequency see first page.

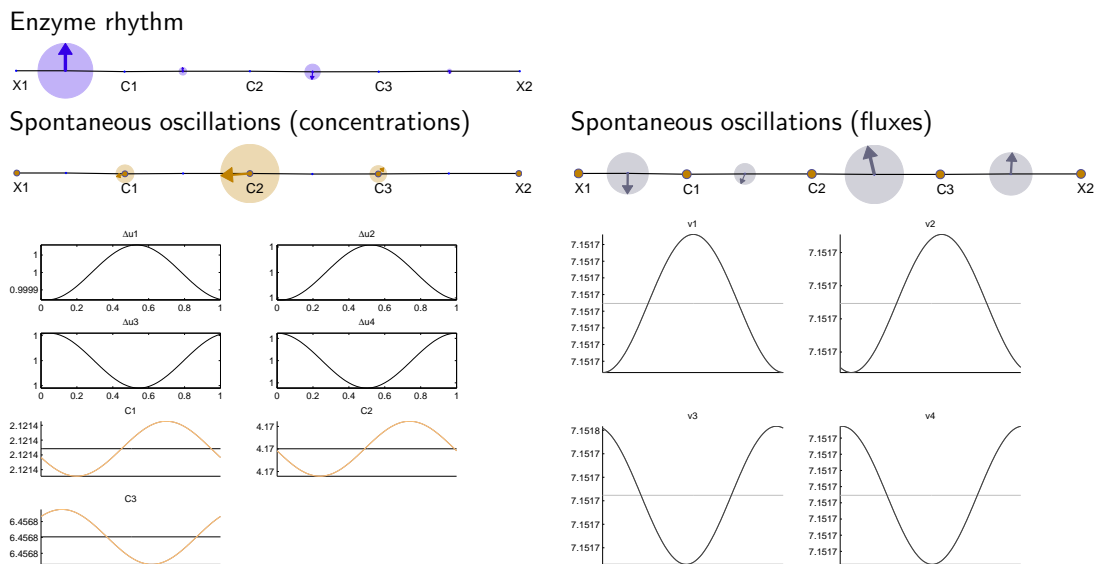
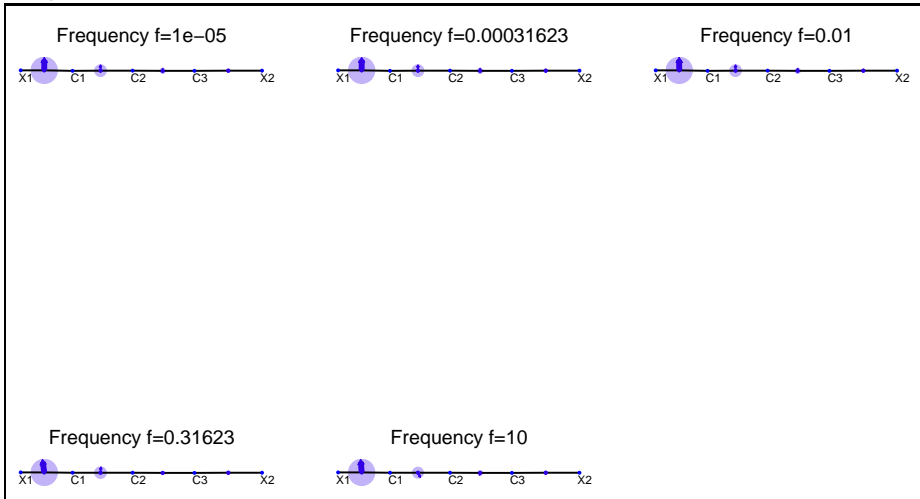


Figure 10: Tentative spontaneous oscillations (local expansion; arrows: absolute changes). Perturbation frequency see first page.

Adaptive



Least costly spontaneous

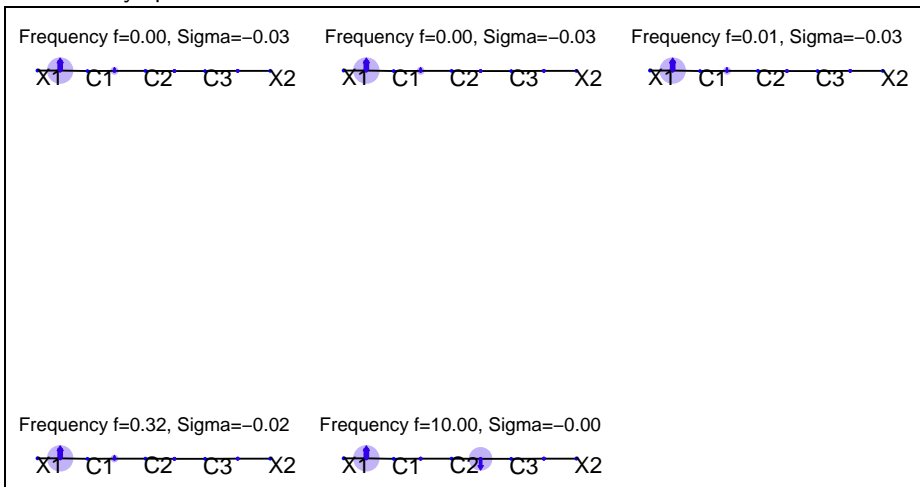


Figure 11: Potential oscillations at various frequencies (local expansion).