

## Enzyme rhythms in model cost\_coupling.speedy

Model name: cost\_coupling

### o Optimisation problem

- Protein turnover time  $1 \text{ s} = 0.0167 \text{ min}$
- Perturbed parameter(s) : x1
- Perturbation frequency  $f : 0.1/\text{s}$  (period 10 s)
- Scored quantity: v1
- Scored quantity: v2
- Fitness-averaged fitness
- No posttranslational rhythms allowed
- Standard frequency considered  $f : 0.1/\text{s}$  (period 10 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 $f=0.1/\text{s}$

- Change by perturbation alone (xx): -0.0418
- Change by adaption synergies (xu): 1.73
- Change by periodic enzyme (uu): -0.413
- Change by enzyme mean shift (u): -3.82e-09
- Total fitness change : 1.28
- Fitness gain by adaption : 1.32
- Maximum adaptive fitness found (in tested range) at frequency  $f=0.01/\text{s}$  (period 100 s)
- Predicted maximal fitness change (adaptive, numeric opt, full amplitude constraints) at frequency  $f=0.01$ : 1.5

### o Self-induced oscillations?

- No beneficial self-induced oscillations (2nd order, amplitude below 1/2 of mean) found at frequency  $f = 0.1/\text{s}$  (principal synergy = -0.005): Predicted fitness change -0.0837

### o Numerical calculation (responsive, $f=0.1$ )

- Fitness change (fitness-averaged): -0.0418
- Fitness change (state-averaged): 1.06e-12

### o Numerical calculation (adaptive, $f=0.1$ )

- Fitness change (fitness-averaged): 1.31
- Fitness change (state-averaged): 1.88

### o Numerical calculation (self-induced rhythm, amplitude below 1/2 of mean, $f=0.1$ )

- Fitness change (fitness-averaged) : 9.11e-13
- Fitness change (state-averaged): -3.02e-14

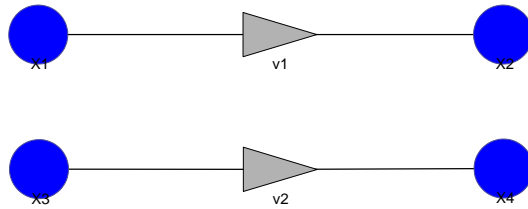


Figure 1: Network and reference flux

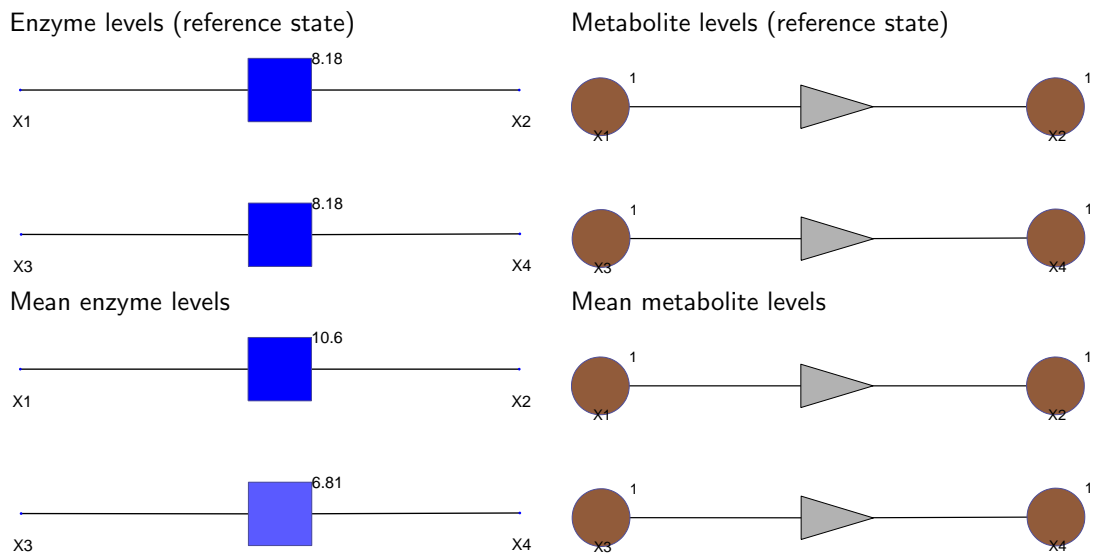


Figure 2: Reference state (top) and mean state during oscillation (bottom).

Jacobian eigenvalues at reference state

Maximal inverse absolute Jacobian eigenvalue

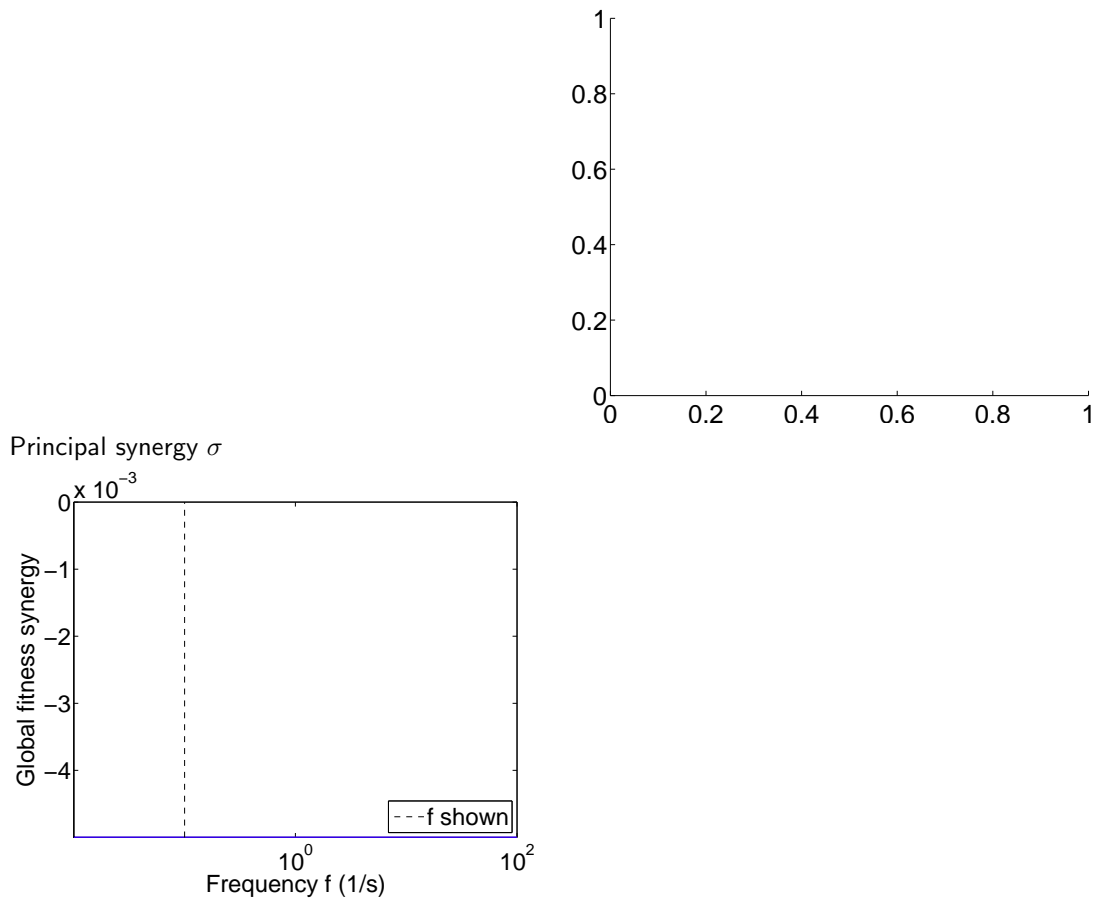
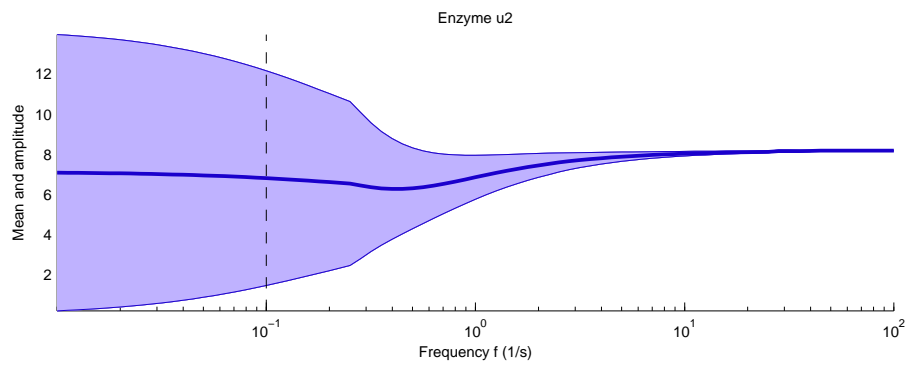
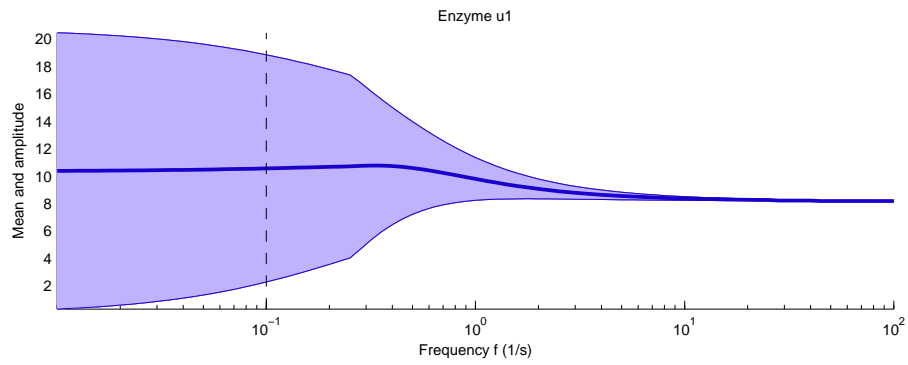
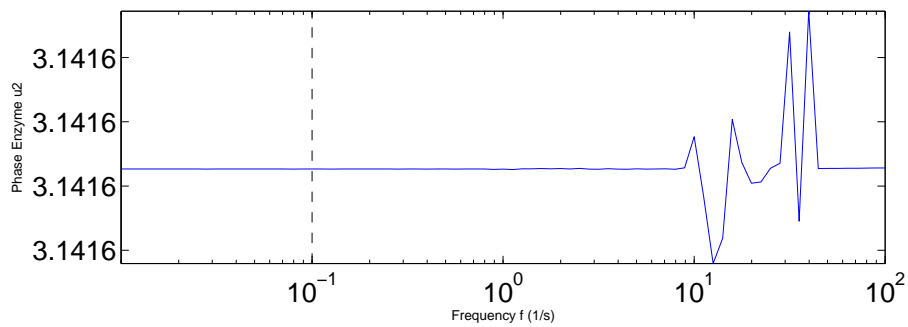
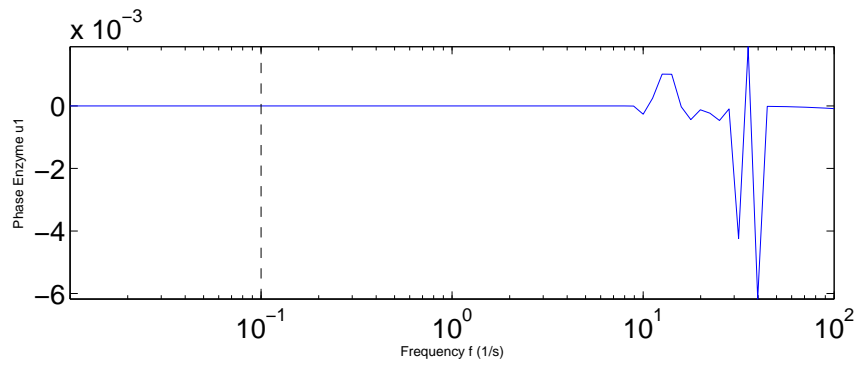


Figure 3: Control analysis. Left: Global fitness synergy (maximal fitness curvature eigenvalue), as a function of the frequency. Right: Relative amplitudes of individual enzymes for the least wasteful enzyme mode (components of the leading fitness curvature eigenvector).

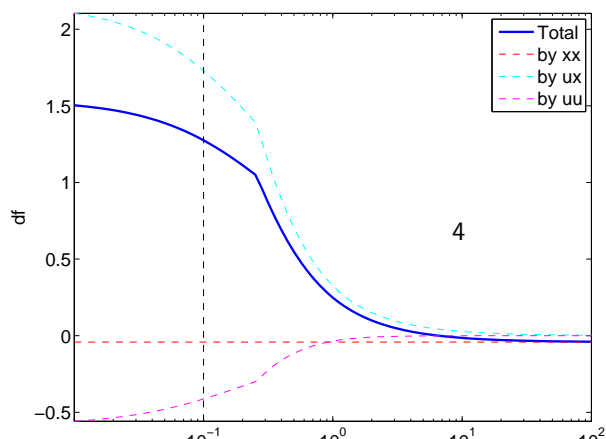
### Protein level and enzyme activity (mean and amplitude)



### Phase angles $[0, 2\pi]$



### Fitness change



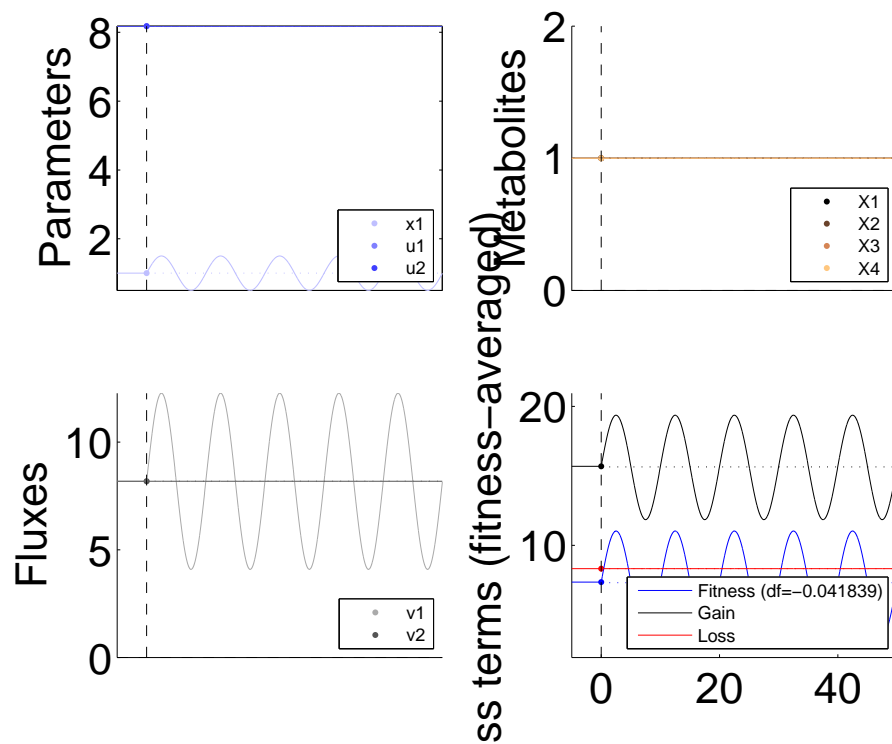


Figure 5: Numerical calculations: responsive oscillations (curves). Dynamic effects of oscillations. The panels show different types of variables: (i) Optimal periodic enzyme levels; (ii) internal metabolite levels; (iii) reaction fluxes; (iv) fitness, benefit, and cost. Perturbation frequency see first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

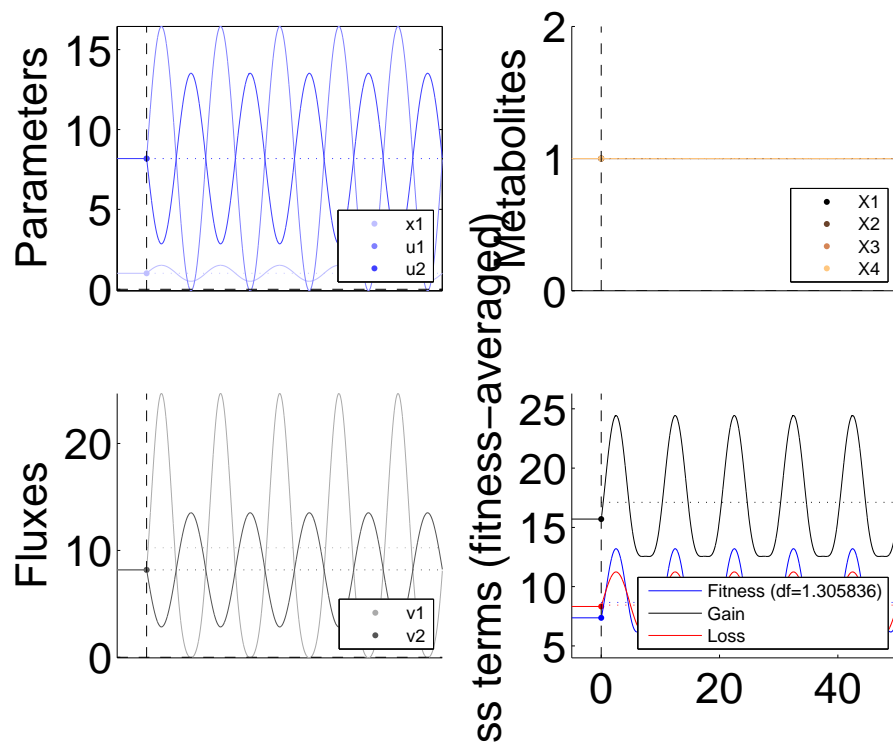


Figure 6: Numerical calculations: adaptive oscillations (curves). Dynamic effects of oscillations. The panels show different types of variables: (i) Optimal periodic enzyme levels; (ii) internal metabolite levels; (iii) reaction fluxes; (iv) fitness, benefit, and cost. Perturbation frequency see first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

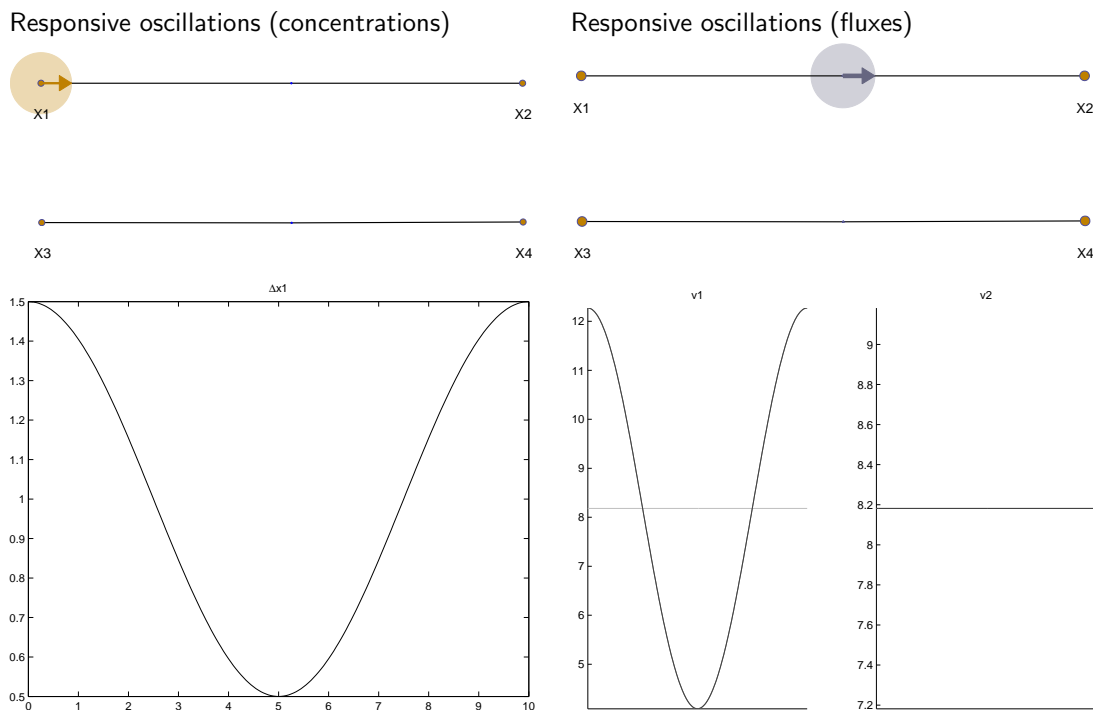
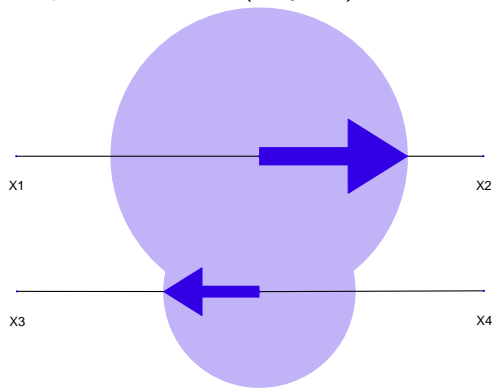
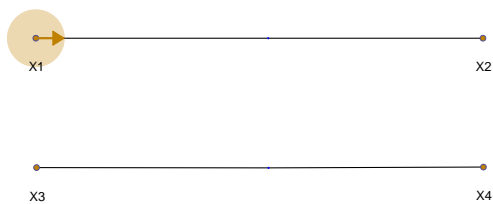


Figure 7: Responsive oscillations (local expansion; arrows: absolute changes) Perturbation frequency see first page.

Adaptive oscillations (enzymes)



Adaptive oscillations (metabolites)



Adaptive oscillations (fluxes)

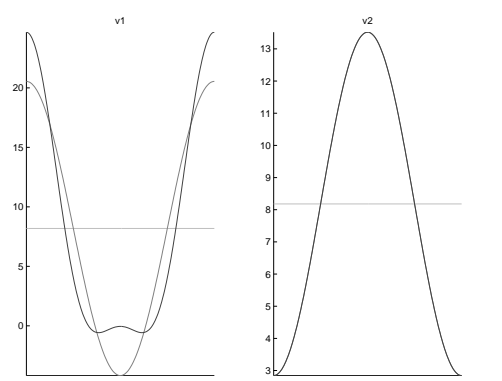
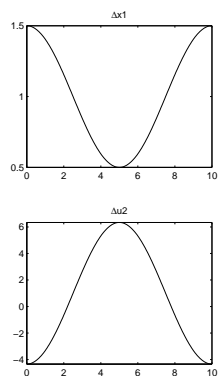
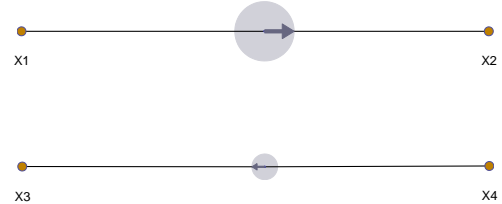


Figure 8: Adaption to forced oscillations (local expansion; arrows: absolute changes). Perturbation frequency see first page.

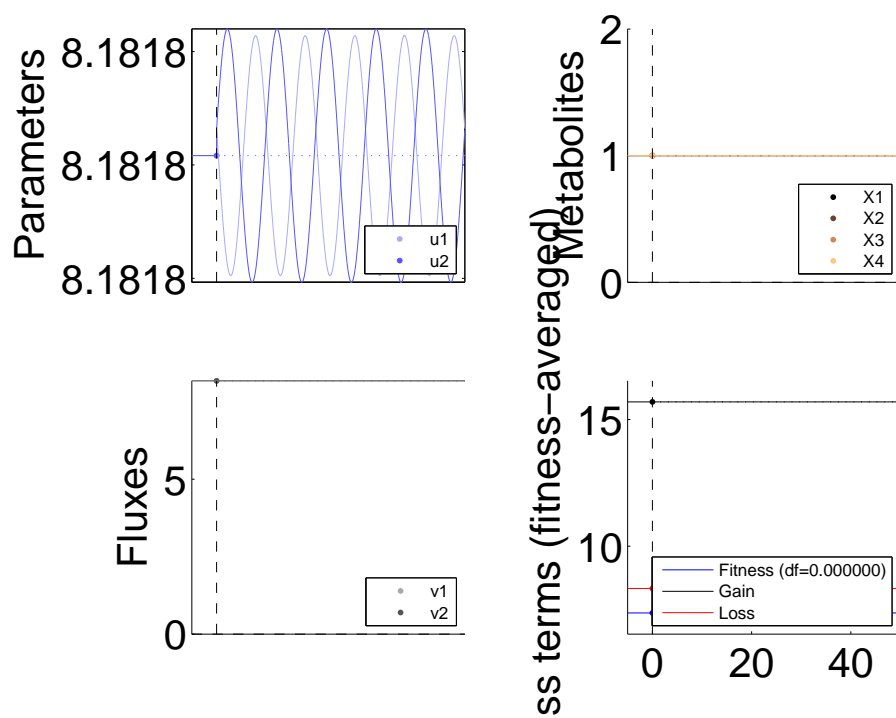
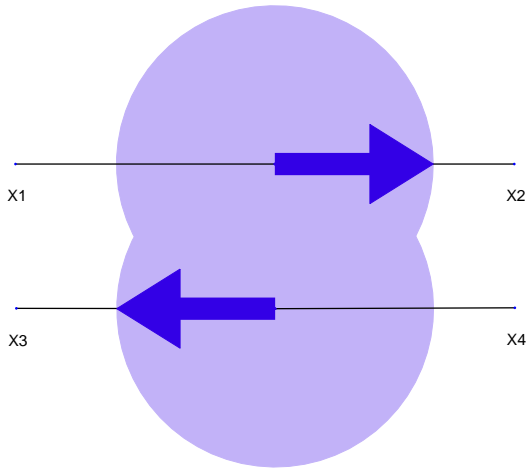


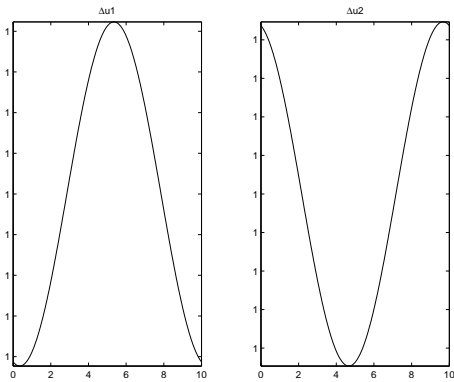
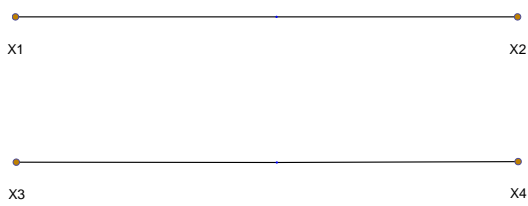
Figure 9: Tentative spontaneous oscillations. Perturbation frequency see first page.



### Enzyme rhythm



### Spontaneous oscillations (concentrations)



### Spontaneous oscillations (fluxes)

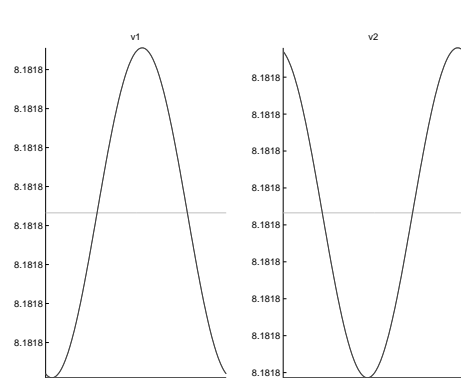
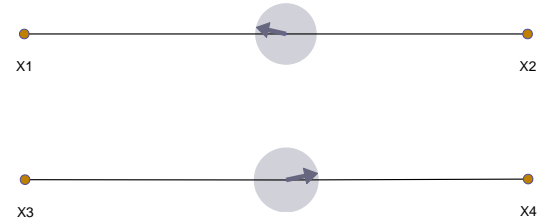
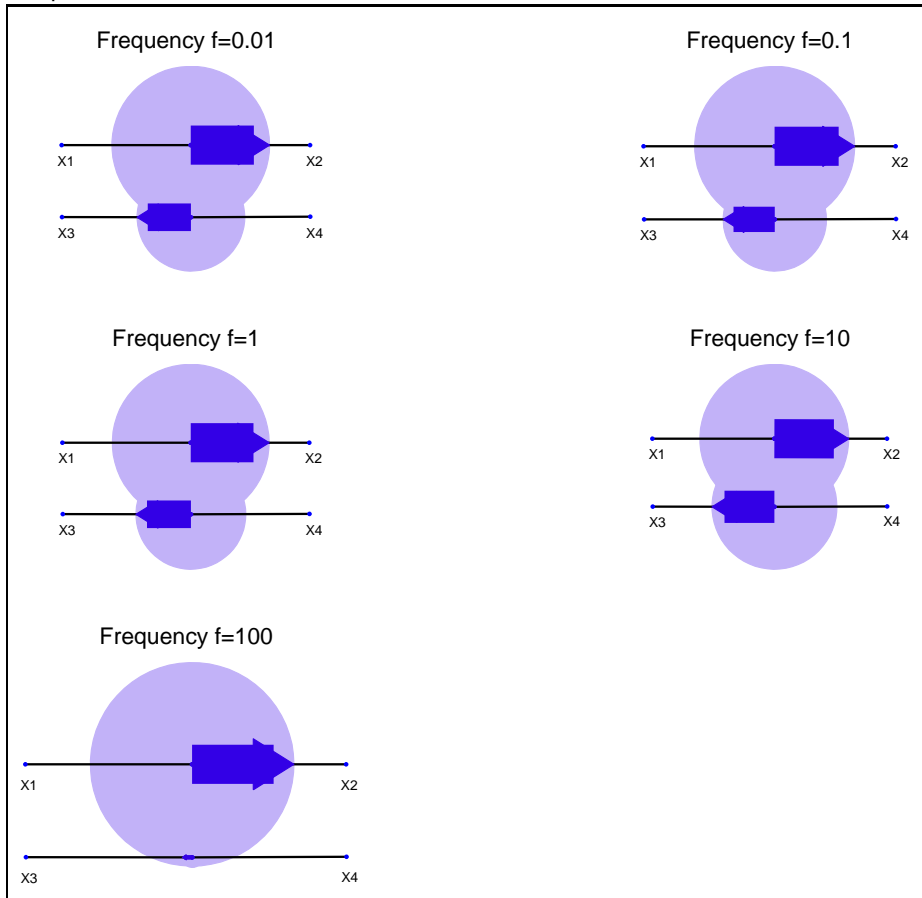


Figure 10: Tentative spontaneous oscillations (local expansion; arrows: absolute changes). Perturbation frequency see first page.

Adaptive



Least costly spontaneous

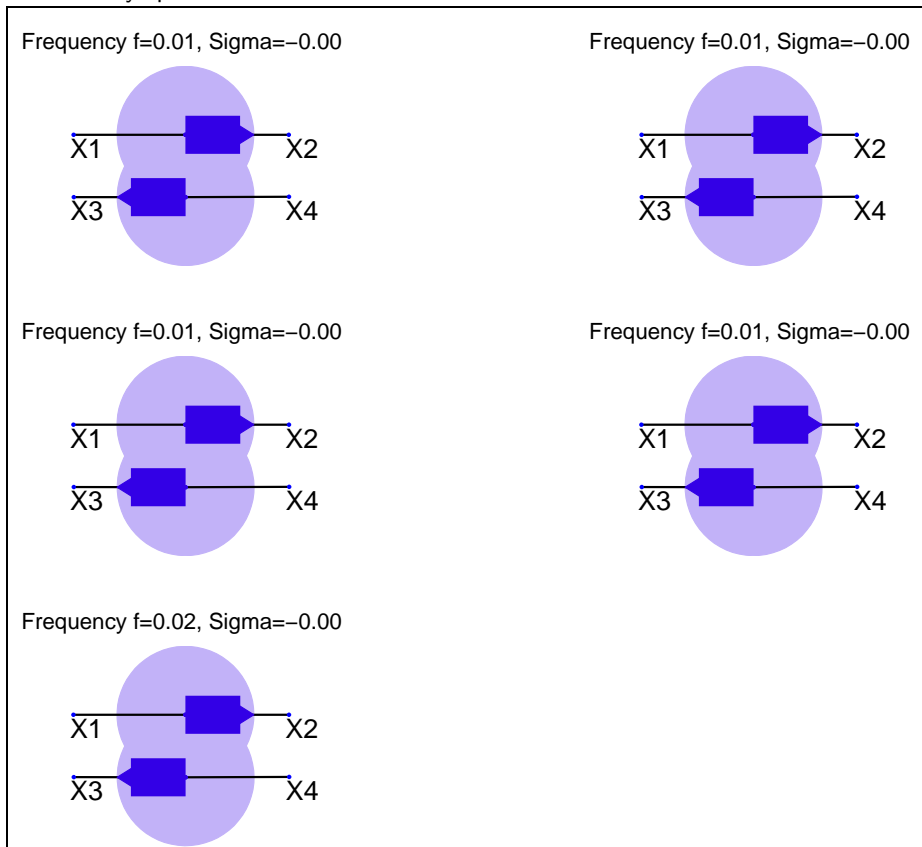


Figure 11: Potential oscillations at various frequencies (local expansion).