Dynamical complexity reduction in biochemical reaction networks

-a time scale decomposition approach-

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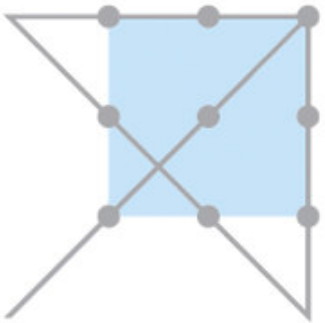


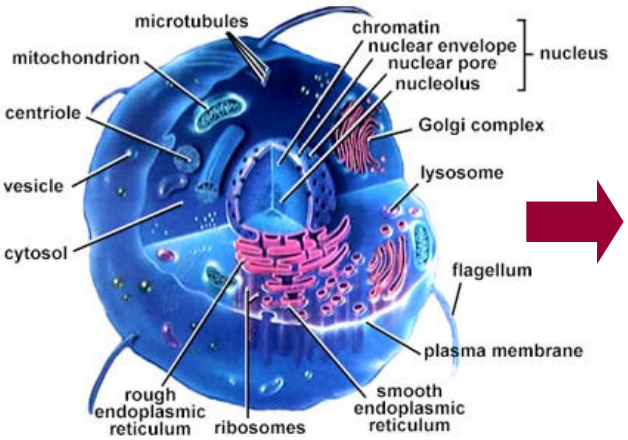
EML Research

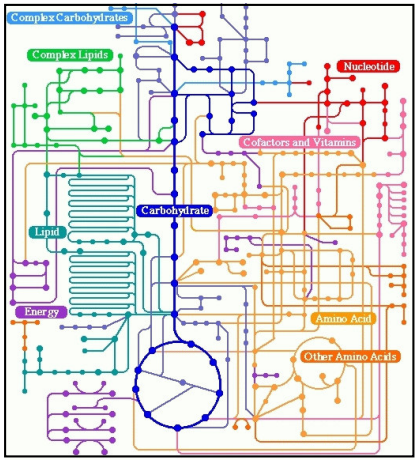
•Outline

- Concepts:
  - Modeling / simulation of biochemical reaction networks
  - Complexity reduction
  - Time scale decomposition (TSD)
- Method:
  - an automated dynamical TSD approach
- Application / Results:
  - TSD in the Peroxidase-Oxidase (PO) reaction network
- Conclusions

•Concepts

➢ Modeling / simulation of biochemical reaction networks





state:

$$\vec{c}(t) = (c_1(t), \ldots, c_N(t))^T$$

dynamics (state transition):

$$\frac{d\vec{c}(t)}{dt} = \vec{f}(\vec{c}(t), \vec{k}) = \mathbf{N} \cdot \vec{v}(\vec{c}(t), \vec{k})$$

cellular system | biochemical reaction network | mathematical description

E. coli:
#genes (total)=4288
#genes (metab.)=660
#enzymes (metab.)=697
#reactions (metab.)=739
#metabolites=442

size and *complexity* of biochem. reaction networks

need for *complexity reduction* methods in order to:

-enable efficient computation of system dynamics
-facilitate identification of dynamical key features

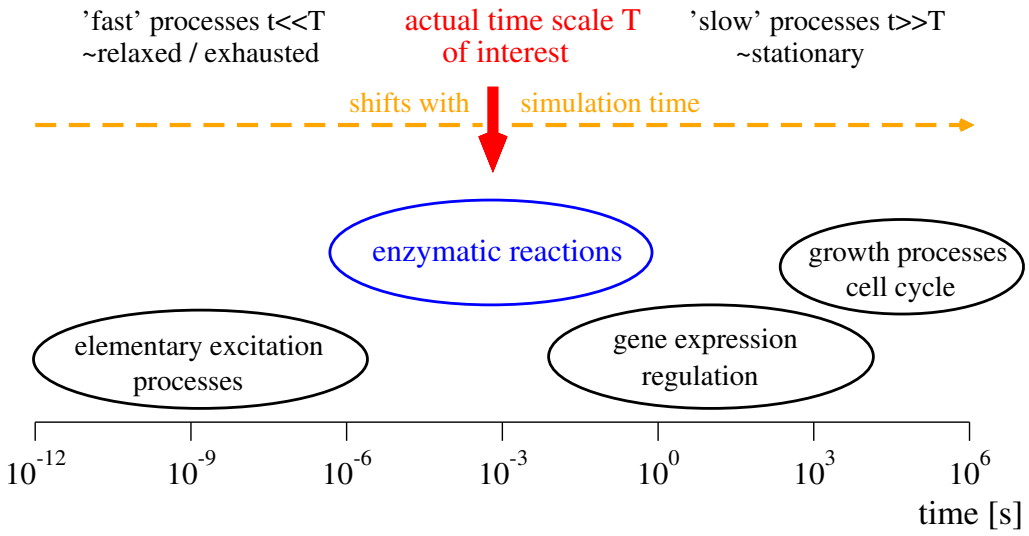
•Concepts

➢ Complexity reduction

- *structural* approaches: based on evaluation of network structure / topology only → limited analytical scope
- *dynamical* approaches: explicitly considering kinetics of individual processes / reactions → in principle full analytical scope

  problem: existing methods rely on specific restrictions on system dynamics like the *steady state* assumption (e.g. SNA) or the *quasi-steady state approximation* (QSSA) → limited applicability

➢Time scale decomposition (TSD)



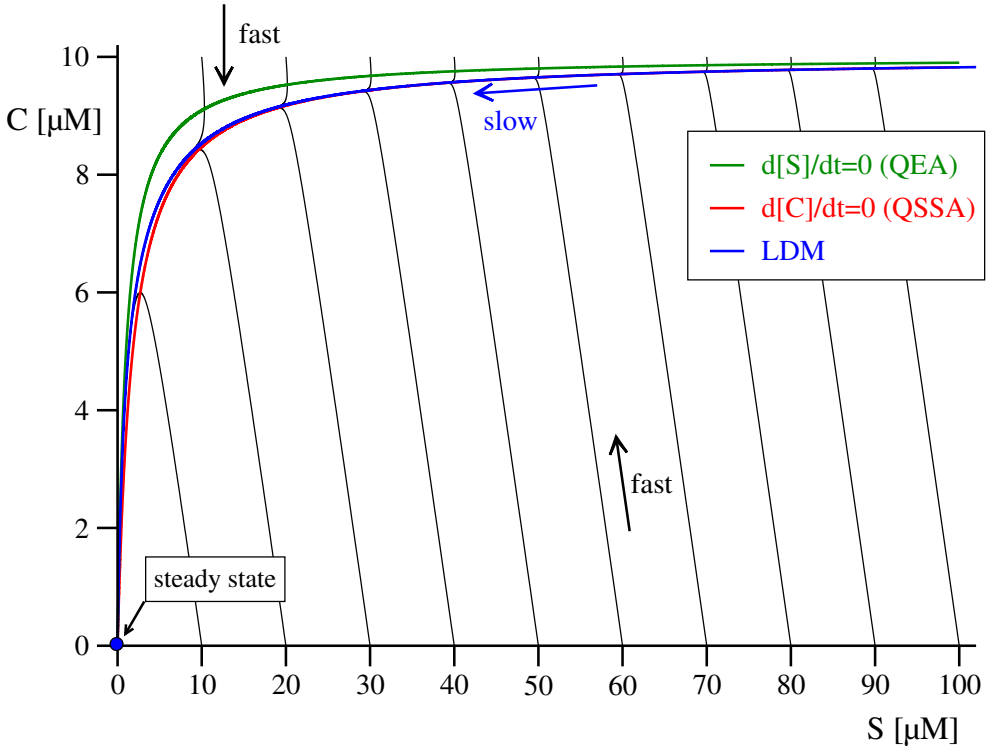
-*dynamical* network partitioning according to *characteristic multiple time scales* of cellular processes spanning several orders of magnitude

•Concepts

➢ Time scale decomposition (TSD)

-dynamics of simple enzyme catalyzed reaction taking place on *two largely differing* time scales

$$S + E \rightleftharpoons C \rightarrow P + E$$



-*fast* time scale: dynamics in *full* 2d phase space
-*slow* time scale: trajectories attracted by *low-dimensional manifold (LDM)* → *reduced* 1d phase space

-conventional TSD approaches:
quasi-steady state approx. (QSSA)
quasi-equilibrium approx. (QEA)

➡

-approach LDM for restricted range of dynamics only
-partitioning based on identification of reactive intermediates / fast reactions

•Method / Objectives

➢ TSD approach for dynamical complexity reduction

- *systematic* reduced description for *arbitrary* biochemical reaction networks (ODE models)
- working *independent* of the assumption of a specific system dynamics / dynamical regime (e.g. steady state)
- *fully automated* network decomposition without *a priori* identification of reactive intermediates / fast reactions (no expert knowledge)
- systematic accuracy criterion / *error control* mechanism → user
- *efficient* implementation / applicable for spatially non-homogeneous model systems

➢ approach based on ILDM method by U. Maas and B. Pope (combustion)

•Method / TSD approach

1) starting point: $\frac{d\vec{c}(t)}{dt} = \vec{f}(\vec{c}(t), \vec{k}), \quad \vec{c}(t=0) = \vec{c}_0$ ODE system (dim. *N*)

2) local system reduction / decomposition

- linearization $\frac{d\vec{c}(t)}{dt} = \vec{f}(\vec{c}_r) + \mathbf{J}_{\vec{c}_r} \cdot (\vec{c}(t) - \vec{c}_r), \quad \mathbf{J}_{\vec{c}_r} = \frac{\partial \vec{f}(\vec{c}_r)}{\partial \vec{c}_r}$ Jacobian matrix

- basis transformation $\left(\vec{c} \xrightarrow{\mathbf{T}_n^{-1}} \vec{x}, \quad \vec{f} \xrightarrow{\mathbf{T}_n^{-1}} \vec{g}\right)$

$$\mathbf{T}_n^{-1} \cdot \mathbf{J} \cdot \mathbf{T}_n = \mathbf{S} = \begin{pmatrix} \mathbf{S}_{slow} & \mathbf{0} \\ \mathbf{0} & \mathbf{S}_{fast} \end{pmatrix}$$ Block-Diagonalization of **J**

reordering of **S** according to characteristic *time scales* $\tau_i = \frac{1}{|\Re(S_{ii})|}$

➢decoupling of reaction system into:
- *n active* (*slow*) processes / modes
- *N-n inactive* (*fast*) processes

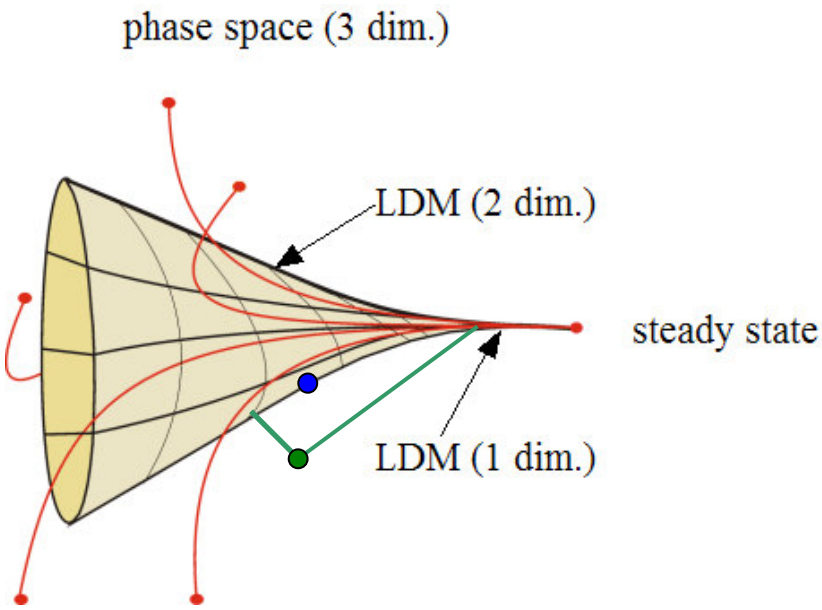
$$\vec{x} = \begin{pmatrix} \vec{x}_{slow} \\ \vec{x}_{fast} \end{pmatrix} = \mathbf{T}_n^{-1} \cdot \vec{c}, \quad \vec{g} = \begin{pmatrix} \vec{g}_{slow} \\ \vec{g}_{fast} \end{pmatrix} = \mathbf{T}_n^{-1} \cdot \vec{f}$$

$$\frac{d\vec{x}_{slow}(t)}{dt} = \vec{g}_{slow}, \quad \frac{d\vec{x}_{fast}(t)}{dt} = \vec{g}_{fast}$$

•Method / TSD approach

2) local system reduction / decomposition

- choice of slow / fast partitioning



➢ ideal case: $\vec{g}_{fast} = \vec{0}$ ●
fast time scales *<u>fully</u>* relaxed,for given partitioning *n* point located on *Intrinsic Low-dimensional manifold (ILDM)*

➢ realistic case: $\vec{g}_{fast} \neq 0$ ●
fast time scales *<u>not fully</u>* relaxed, accuracy of reduced system representation for given partitioning *n* depends on size of deviation from ILDM
→ error criterion / tolerance (user)

number of active modes determined in *iterative procedure*

3) time propagation / integration

- local system reduction: ODE system (dim *N*) → DAE system (*n* ODEs, *N-n* AEs)

➢ <u>full algorithm:</u> for *nonlinear* systems → *sequence* of local decomposition and propagation steps

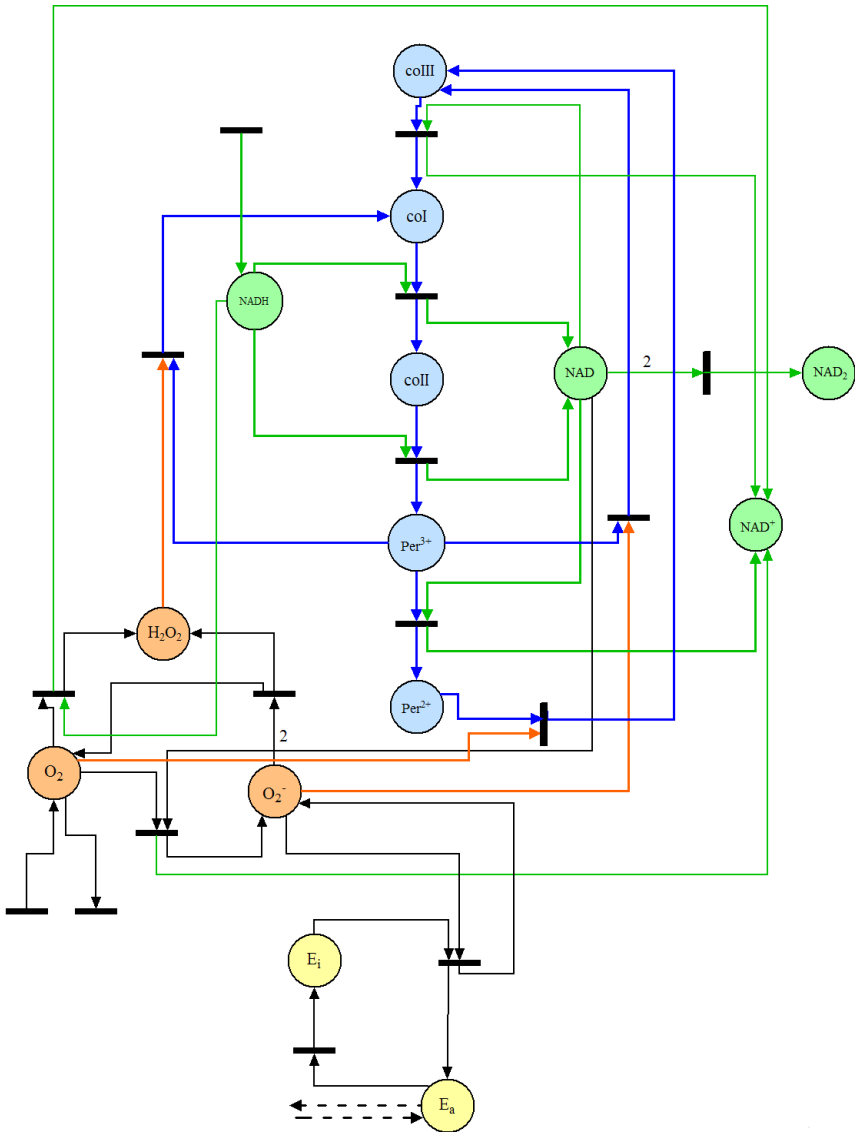
•Application / Results

➢ TSD case study of Peroxidase-Oxidase (PO) reaction network

-kinetic model of PO reaction network coupled to activation of an enzyme E:

reaction	rate expression	constant
(1) $NADH + O_2 + H^+ \longrightarrow NAD^+ + H_2O_2$	$k_1[NADH][O_2]$	3.0 [a]
(2) $H_2O_2 + Per^{3+} \longrightarrow coI$	$k_2[H_2O_2][Per^{3+}]$	1.8×10^7 [a]
(3) $coI + NADH \longrightarrow coII + NAD^{\cdot}$	$k_3[coI][NADH]$	4.0×10^5 [a]
(4) $coII + NADH \longrightarrow Per^{3+} + NAD^{\cdot}$	$k_4[coII][NADH]$	2.6×10^5 [a]
(5) $NAD^{\cdot} + O_2 \longrightarrow NAD^+ + O_2^-$	$k_5[NAD^{\cdot}][O_2]$	2.0×10^7 [a]
(6) $O_2^- + Per^{3+} \longrightarrow coIII$	$k_6[O_2^-][Per^{3+}]$	1.7×10^6 [a]
(7) $2O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2$	$k_7[O_2^-]^2$	2.0×10^7 [a]
(8) $coIII + NAD^{\cdot} \longrightarrow coI + NAD^+$	$k_8[coIII][NAD^{\cdot}]$	11.0×10^7 [a]
(9) $2NAD^{\cdot} \longrightarrow NAD_2$	$k_9[NAD^{\cdot}]^2$	5.6×10^7 [a]
(10) $Per^{3+} + NAD^{\cdot} \longrightarrow Per^{2+} + NAD^+$	$k_{10}[Per^{3+}][NAD^{\cdot}]$	1.8×10^6 [a]
(11) $Per^{2+} + O_2 \longrightarrow coIII$	$k_{11}[Per^{2+}][O_2]$	1.0×10^5 [a]
(12) $\longrightarrow NADH$	k_{12}	*variable*
(13) $O_2(gas) \longrightarrow O_2(liquid)$	$k_{13}[O_2]_{eq}$	4.4×10^{-3} [c,d]
(−13) $O_2(liquid) \longrightarrow O_2(gas)$	$k_{-13}[O_2]$	4.4×10^{-3} [c]
(14) $Enz_{inact} + O_2^- \longrightarrow Enz_{act}$	$\frac{k_{14}[O_2^-]^5}{(K_f^5+[O_2^-]^5)}$	0.005 [a] (k_{14})
		0.4 [b,e] (K_f)
(15) $Enz_{act} \longrightarrow Enz_{inact}$	$k_{15}[Enz_{act}]$	1.6 [c]

Detailed model of the Peroxidase–Oxidase (PO) reaction network coupled to the activation of an enzyme *Enz* ([a] in $M^{-1}s^{-1}$, [b] in M, [c] in s^{-1}, [d] $[O_2]_{eq} = 1.2 \times 10^{-5}$ M, [e] $[Enz_{act}] << Enz_{inact} \approx$ const.).

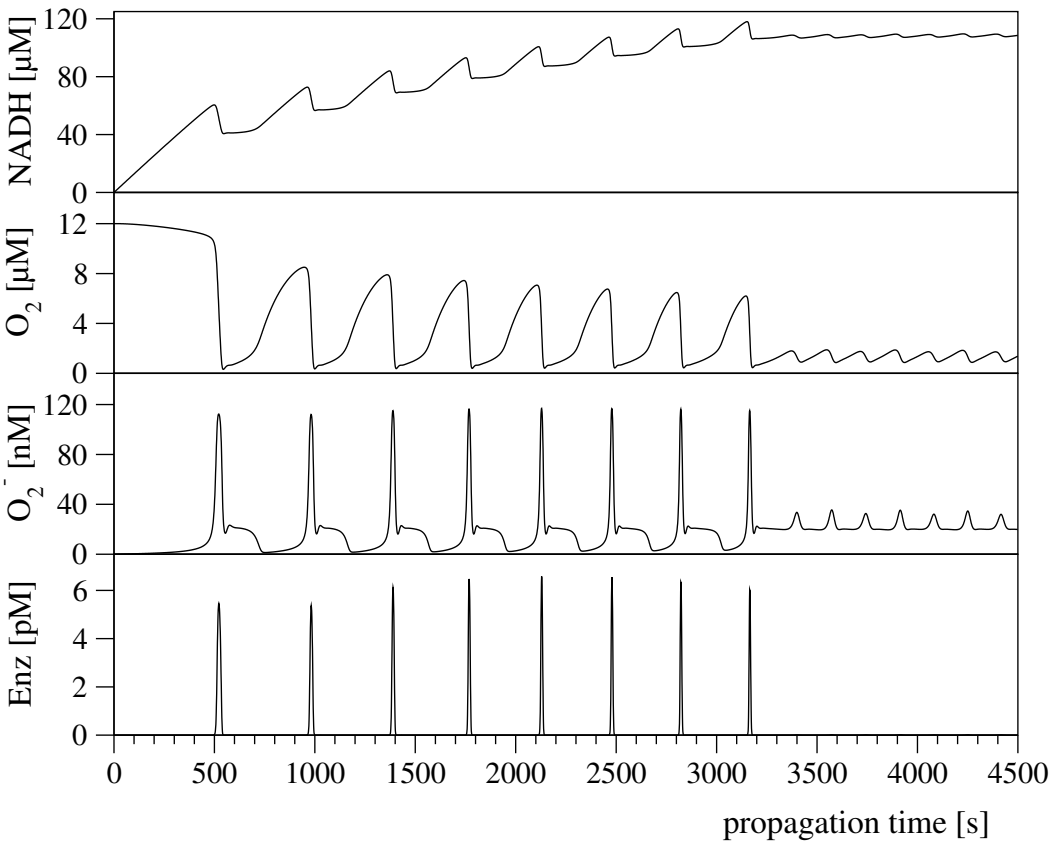


-production of reactive oxygen species (ROS)
→ important role in pathogen defense of activated neutrophils
-large variety in dynamical behavior:
steady state - regular / relaxation oscillations - chaos

•Application / Results

➢ dynamics of the PO reaction network

- simulated time series for selected species of the PO reaction network (k_{12}=0.129 µM/s)



dynamical capabilities depending sensitively on NADH inflow rate

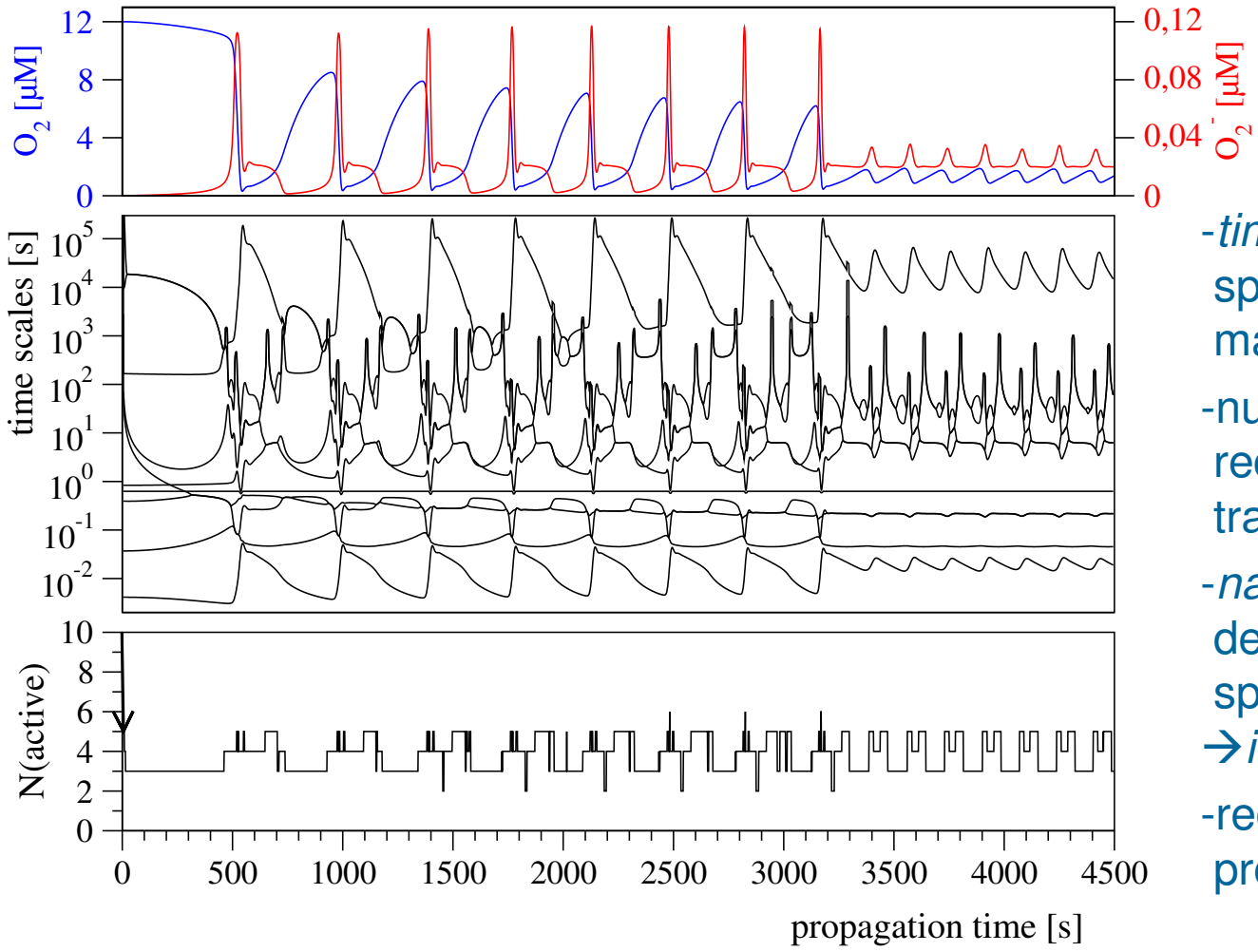
t<3200s: transient large amplitude relaxation oscillations

t>3200s: sustained small amplitude regular oscillations

t≈3200s: dynamical switching off of enzyme activation

•Application / Results

➢ time scale decomposition of the PO reaction network

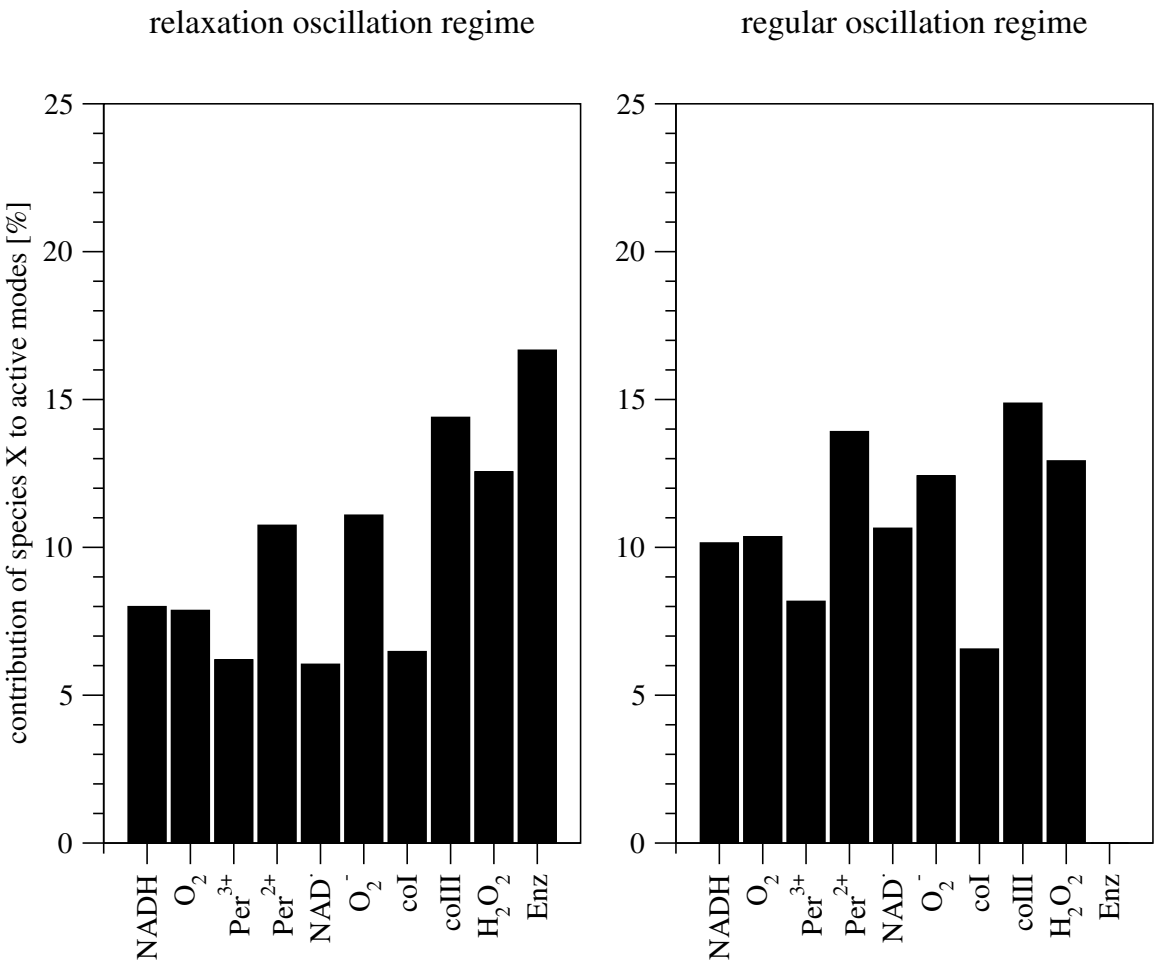


- *time scales* of processes spanning **7- 8** orders of magnitude
- number of *active modes* reduced drastically along trajectory: **11 → 6 - 2 / 5 - 3**
- *nature* of decomposition depends sensitively on specific dynamical regime *→insight into reaction mech.*
- reduced *stiffness*→ efficient propagation

•Application / Results

➢ time scale decomposition of the PO reaction network

- analysis of the active processes / modes in terms of contributing



$$\vec{x}_{\text{slow}} = \mathbf{T}_{\mathbf{r,slow}}^{-1} \cdot \vec{c}$$

→ automated detection of dynamical network partitioning (dynamical coupling / decoupling)

•Conclusions

- The presented TSD method based on the ILDM approach
  - is well suited for the dynamical complexity reduction of biochemical reaction networks even in demanding cases of complex system dynamics
  - provides a fully automated, adapted dynamical network decomposition for all dynamical regimes of nonlinear reaction systems
  - simplifies identification of dynamical key features of complex reaction networks
  - can be adapted for efficient simulation of non-homogeneous reaction systems in straightforward manner following discretization

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