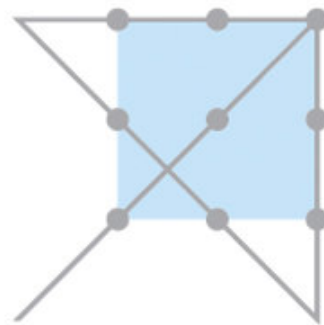


Dynamical complexity reduction in biochemical reaction networks

-a time scale decomposition approach-

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EML
R e s e a r c h

•Outline

➤ Concepts:

- Modeling / simulation of biochemical reaction networks
- Complexity reduction
- Time scale decomposition (TSD)

➤ Method:

- an automated dynamical TSD approach

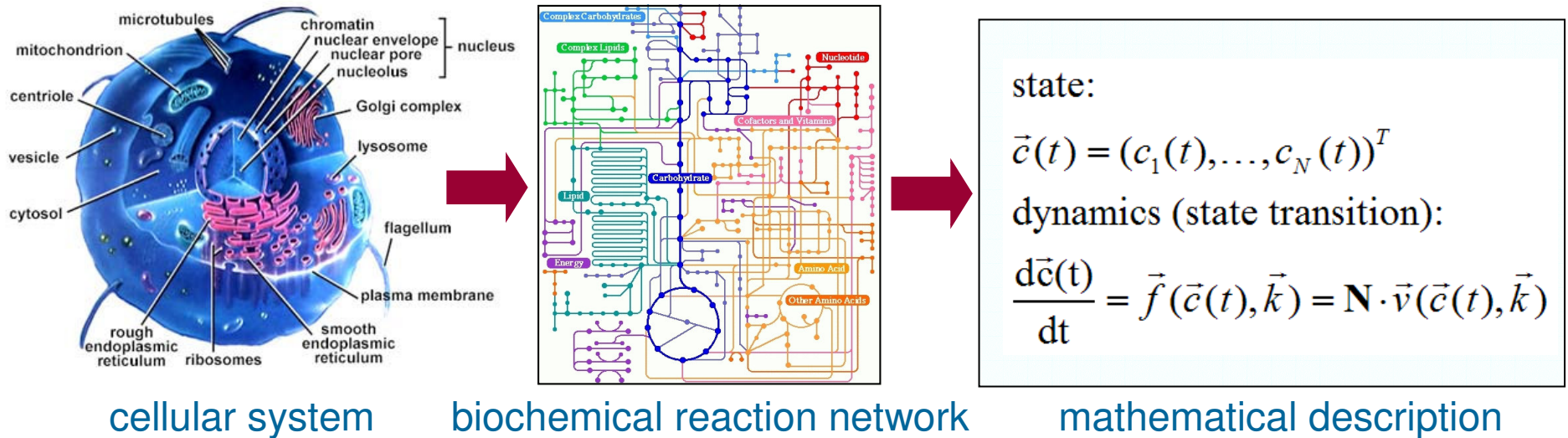
➤ Application / Results:

- TSD in the Peroxidase-Oxidase (PO) reaction network

➤ Conclusions

•Concepts

➤ Modeling / simulation of biochemical reaction networks



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

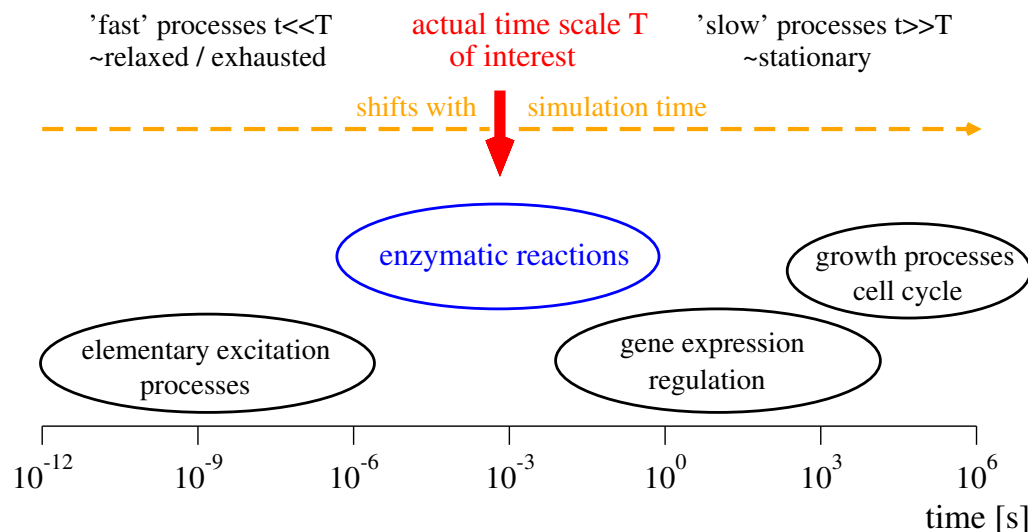
•Concepts

➤ 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)

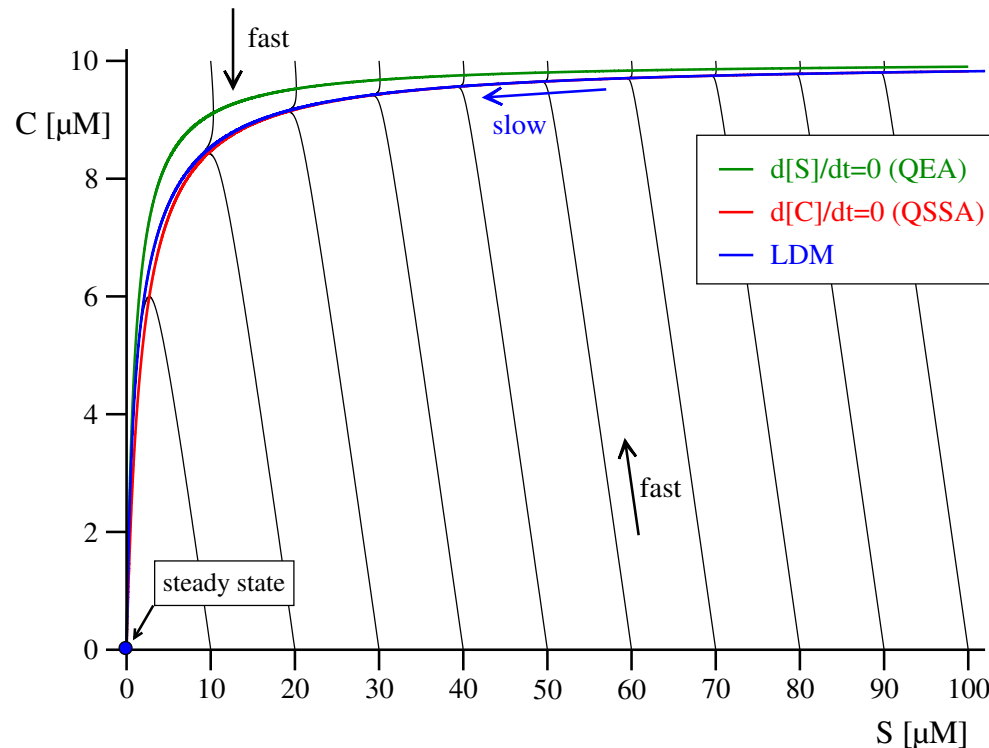
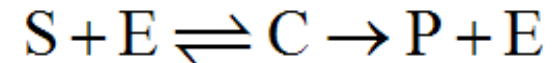


-*dynamical* network partitioning according to *characteristic multiple time scales* of cellular processes spanning several orders of magnitude

•Concepts

➤ Time scale decomposition (TSD)

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



- 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. M)

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

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

reordering of \mathbf{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

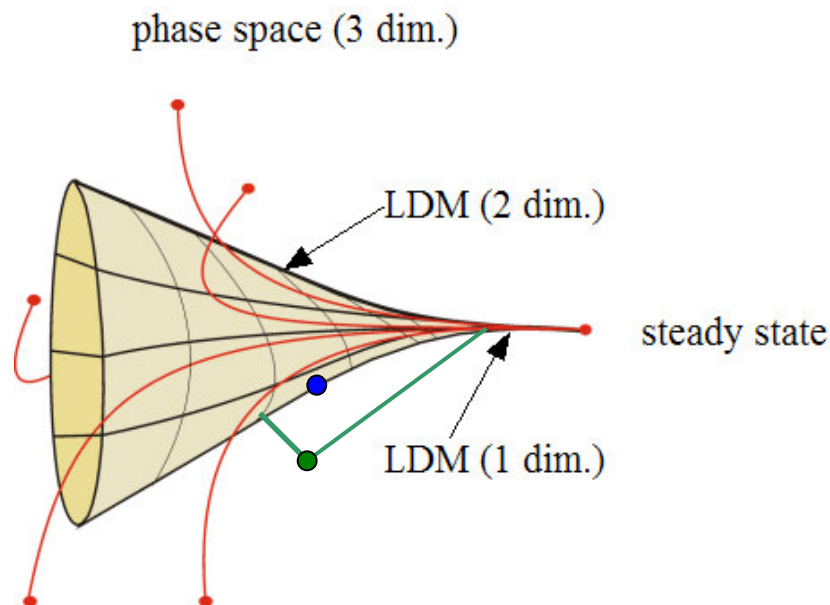
$$\vec{x} = \begin{pmatrix} \vec{x}_{slow} \\ \vec{x}_{fast} \end{pmatrix} = \mathbf{T}_n^{-1} \cdot \vec{c}, \quad \vec{g} = \begin{pmatrix} \vec{g}_{slow} \\ \vec{g}_{fast} \end{pmatrix} = \mathbf{T}_n^{-1} \cdot \vec{f}$$

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

•Method / TSD approach

2) local system reduction / decomposition

- choice of slow / fast partitioning



➤ ideal case: $\vec{g}_{fast} = \vec{0}$ ●

fast time scales fully relaxed, for given partitioning n point located on *Intrinsic Low-dimensional manifold (ILDM)*

➤ realistic case: $\vec{g}_{fast} \neq 0$ ●

fast time scales not fully 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)
- full algorithm: for *nonlinear* systems → *sequence* of local decomposition and propagation steps

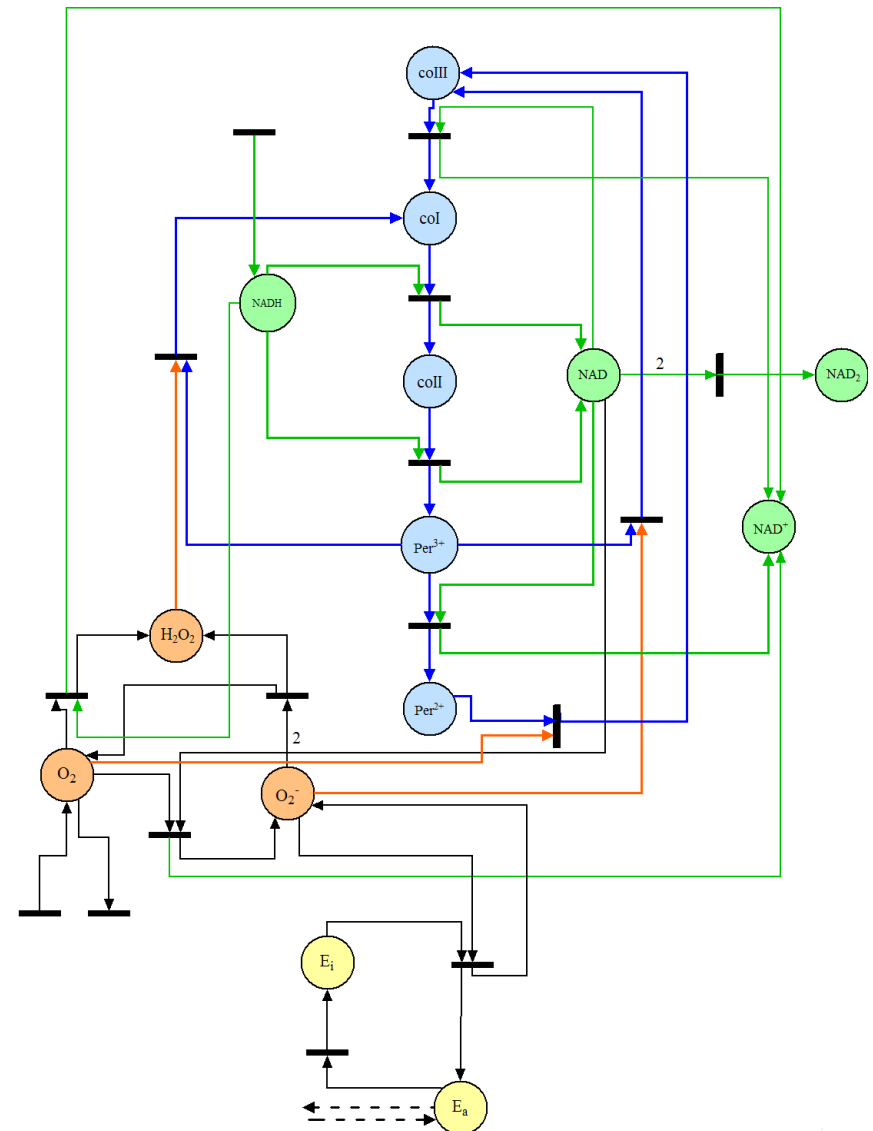
•Application / Results

➤ 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) $NADH + O_2 + H^+ \rightarrow NAD^+ + H_2O_2$	$k_1[NADH][O_2]$	3.0^a
(2) $H_2O_2 + Per^{3+} \rightarrow coI$	$k_2[H_2O_2][Per^{3+}]$	$1.8 \times 10^7^a$
(3) $coI + NADH \rightarrow coII + NAD^+$	$k_3[coI][NADH]$	$4.0 \times 10^5^a$
(4) $coII + NADH \rightarrow Per^{3+} + NAD^+$	$k_4[coII][NADH]$	$2.6 \times 10^5^a$
(5) $NAD^+ + O_2 \rightarrow NAD^+ + O_2^-$	$k_5[NAD^+][O_2]$	$2.0 \times 10^7^a$
(6) $O_2^- + Per^{3+} \rightarrow coIII$	$k_6[O_2^-][Per^{3+}]$	$1.7 \times 10^6^a$
(7) $2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$	$k_7[O_2^-]^2$	$2.0 \times 10^7^a$
(8) $coIII + NAD^+ \rightarrow coI + NAD^+$	$k_8[coIII][NAD^+]$	$11.0 \times 10^7^a$
(9) $2NAD^+ \rightarrow NAD_2$	$k_9[NAD^+]^2$	$5.6 \times 10^7^a$
(10) $Per^{3+} + NAD^+ \rightarrow Per^{2+} + NAD^+$	$k_{10}[Per^{3+}][NAD^+]$	$1.8 \times 10^6^a$
(11) $Per^{2+} + O_2 \rightarrow coIII$	$k_{11}[Per^{2+}][O_2]$	$1.0 \times 10^5^a$
(12) $\rightarrow NADH$	k_{12}	<i>variable</i>
(13) $O_2(gas) \rightarrow O_2(liquid)$	$k_{13}[O_2]_{eq}$	$4.4 \times 10^{-3c,d}$
(-13) $O_2(liquid) \rightarrow O_2(gas)$	$k_{-13}[O_2]$	4.4×10^{-3c}
(14) $Enz_{inact} + O_2^- \rightarrow Enz_{act}$	$\frac{k_{14}[O_2^-]^5}{(K_f^5 + [O_2^-]^5)}$	$0.005^a (k_{14})$
(15) $Enz_{act} \rightarrow Enz_{inact}$	$k_{15}[Enz_{act}]$	$0.4^{b,e} (K_f)$
		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 $[Enz_{act}] \ll Enz_{inact} \approx const.$).



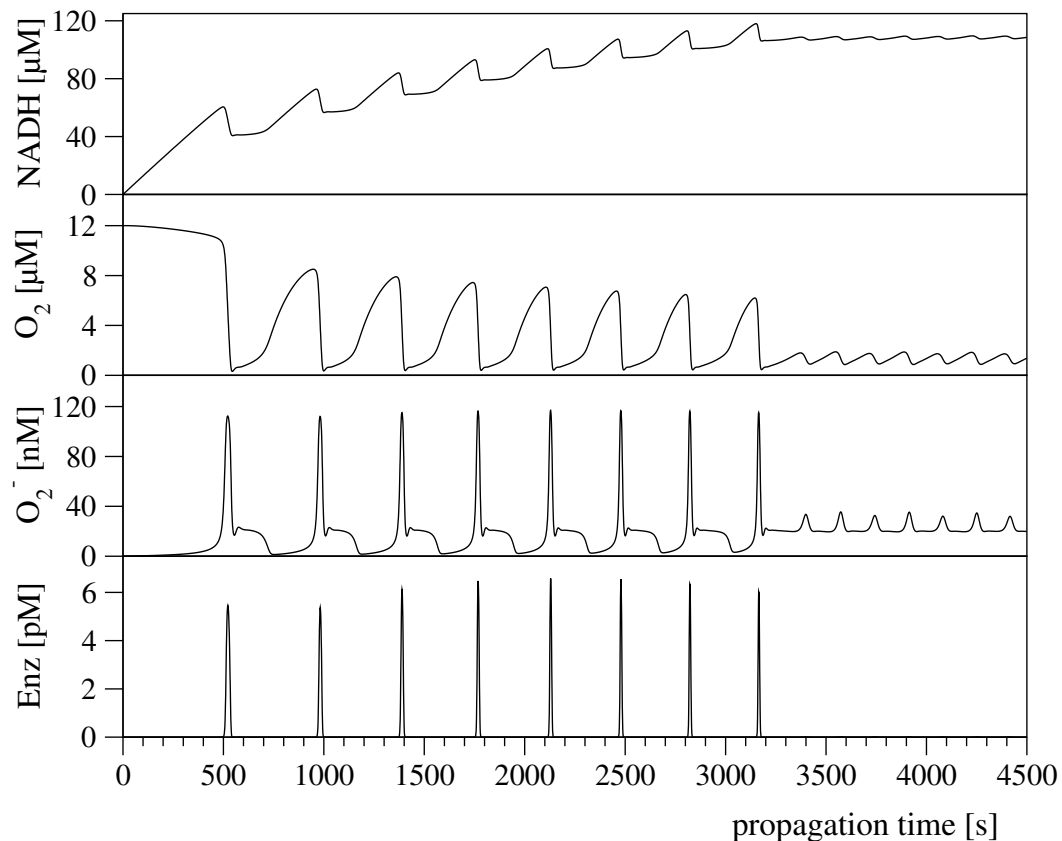
-production of reactive oxygen species (ROS)
 → important role in pathogen defense of activated neutrophils

-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 ($k_{12}=0.129 \mu\text{M/s}$)



dynamical capabilities depending sensitively on NADH inflow rate

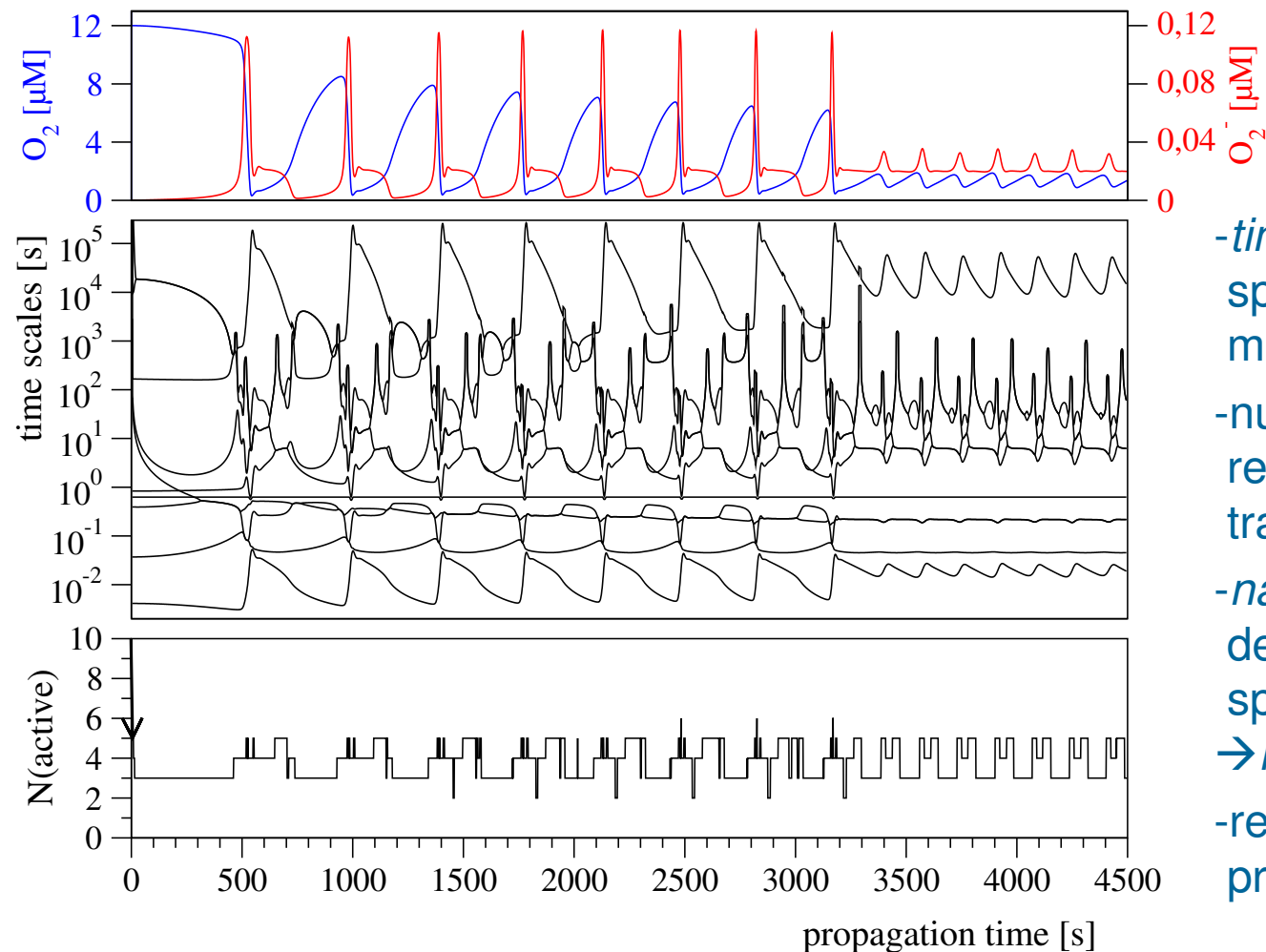
$t < 3200$ s: transient large amplitude relaxation oscillations

$t > 3200$ s: sustained small amplitude regular oscillations

$t \approx 3200$ s: dynamical switching off of enzyme activation

•Application / Results

➤ time scale decomposition of the PO reaction network

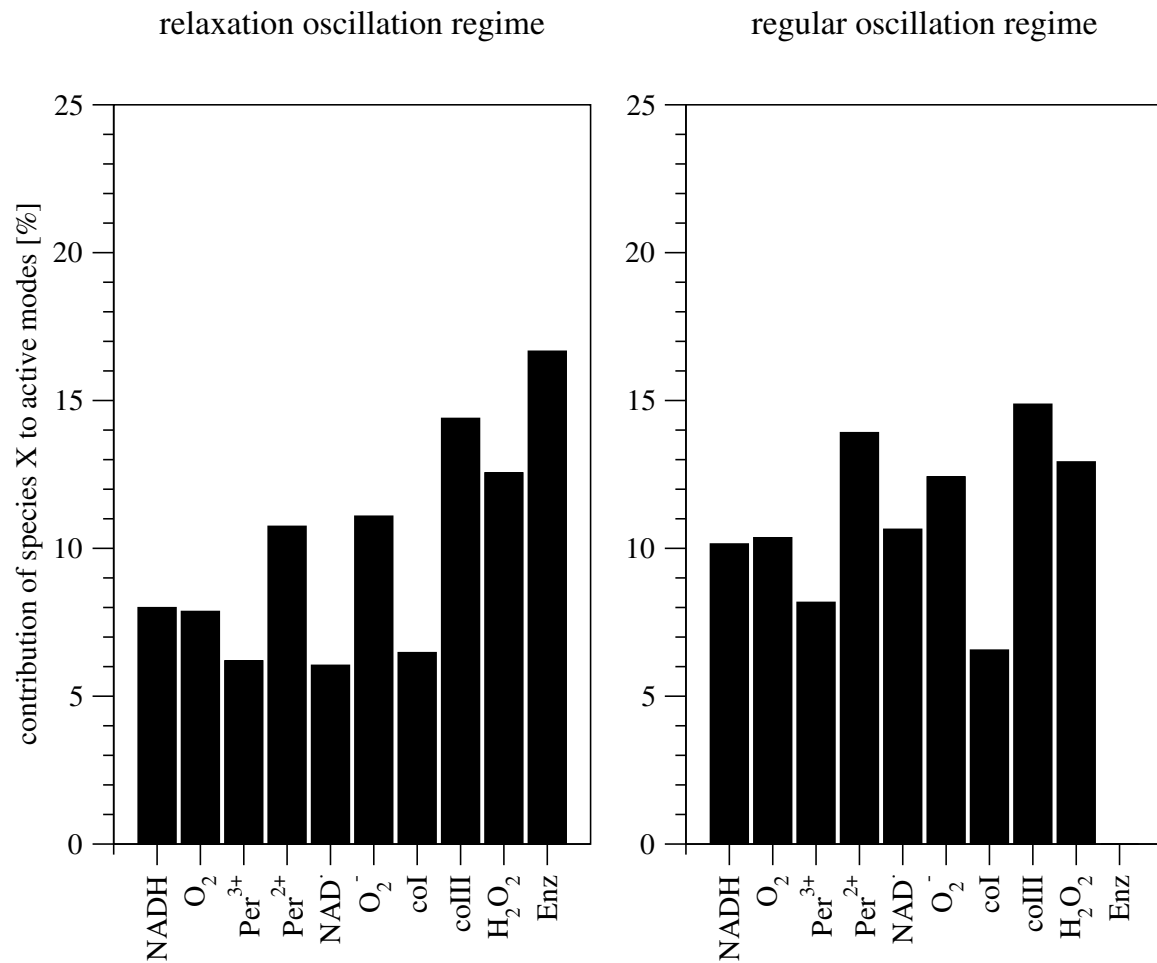


- time scales of processes spanning 7-8 orders of magnitude
- number of *active modes* reduced drastically along trajectory: **11** \rightarrow **6 - 2 / 5 - 3**
- nature* of decomposition depends sensitively on specific dynamical regime
 \rightarrow *insight into reaction mech.*
- reduced *stiffness*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

•Application / Results

➤ time scale decomposition of the PO reaction network

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



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

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

•Conclusions

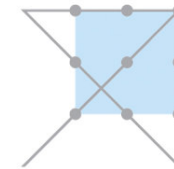
- The presented TSD method based on the ILDM approach
 - is well suited for the dynamical complexity reduction of biochemical reaction networks even in demanding cases of complex system dynamics
 - provides a fully automated, adapted dynamical network decomposition for all dynamical regimes of nonlinear 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

•Acknowledgements

➤ Colaboration partners:

– Ursula Kummer

Bioinformatics and Computational Biochemistry
EML Research gGmbH
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EML
Research

– Dirk Lebiedz

– Julia Kammerer

Interdisciplinary Center for Scientific Computing (IWR)
University of Heidelberg
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➤ Financial support

– Klaus Tschira Foundation gGmbH