The maximum entropy production principle in enzyme kinetics: novel theoretical insights

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Introduction

- Maximum entropy production principle (MEPP) and Shannon information entropy (MaxEnt)
- Enzymes as intrinsically flexible molecules

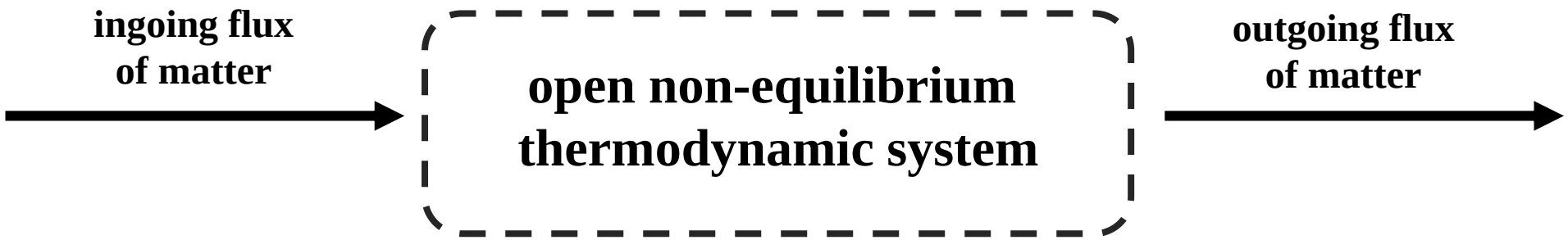
Mathematical model

-Entropy production
-Shannon information entropy
-Enzyme kinetic flexibility

Model results and discussion

Conclusions

Enzyme reactions as open non-equilibrium systems



Maximum entropy production principle (MEPP)

An open non-equilibrium thermodynamic system tend spontaneusly towards non-equlibrium steady state (NESS) characterised by maximal entropy production.

Among all possible NESS the steady state of MEP is selected because it is statistically most probable.

most uniform distribution of microscopic states of the system → **maximal Shannon information entropy**

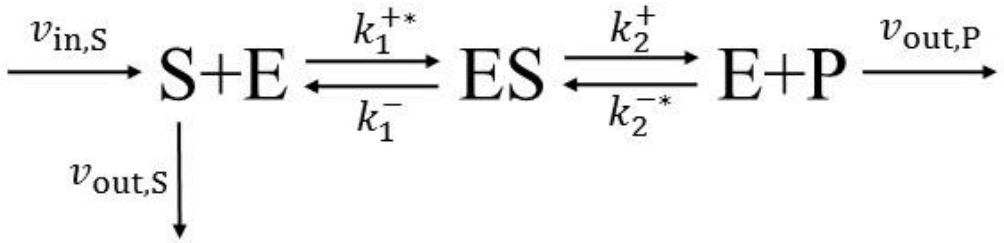
Enzymes are intrinsically flexible molecules

Flexible nature of enzyme structure has been recognized, established and accepted as a fundamental property with mayor consequences to their function (kinetics).

$$S+E \underset{k_1^-}{\overset{k_1^{+*}}{\rightleftharpoons}} ES \underset{k_2^{-*}}{\overset{k_2^{+}}{\rightleftharpoons}} E+P$$

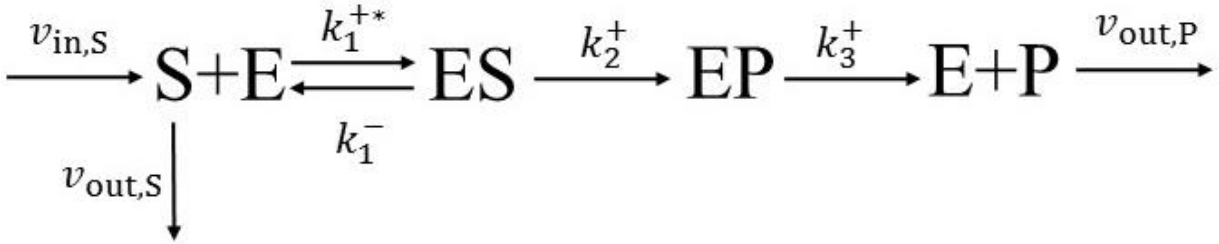
Enzymes under consideration

Glucose Isomerase (GI)



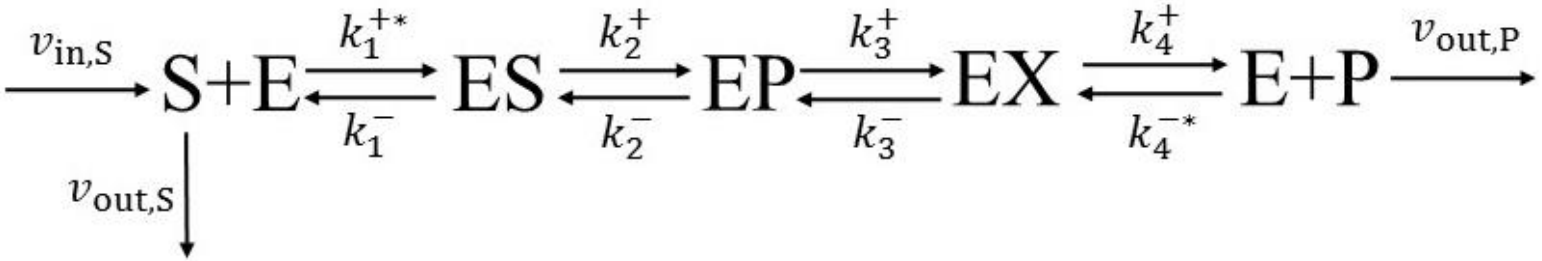
Production of high fructose corn syrup in continuos stirred tank reactors.

β – Lactamase



Bacterial resistance to β – lactam antibiotics.

Triosephosphate isomerase



Glycolysis

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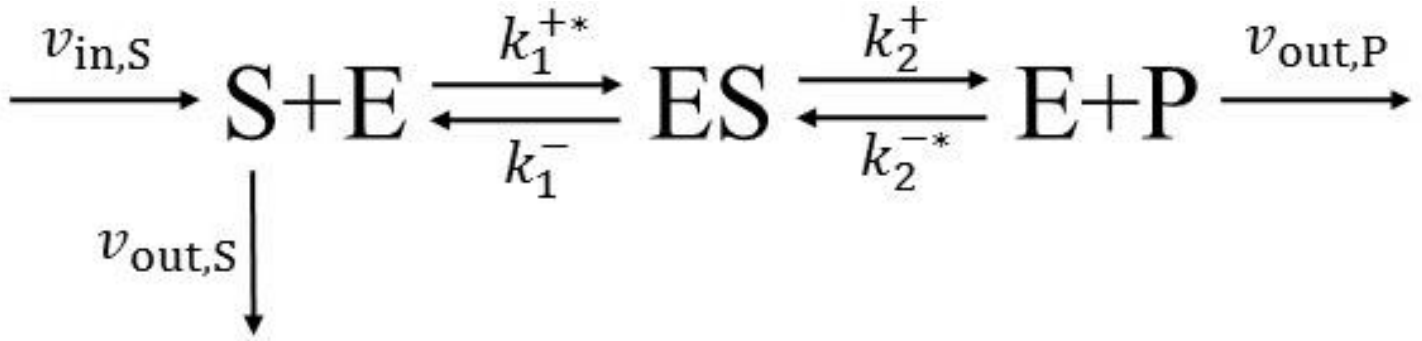
Mathematical modelling
(Model for GI)



Constraints

1. Mass conservation of a reaction system

2. Fixed equilibrium constant of a reaction

$$K^* = \frac{k_1^{+*} k_2^+}{k_1^- k_2^{-*}} = const.$$

Density of entropy production

$$\sigma = \frac{\nu X}{T}$$

$$X = RTln\left(K^* \frac{[S]_{\text{SS}}}{[P]_{\text{SS}}}\right)$$

$$v = \frac{[E]_{\text{tot}}(k_1^{+*} k_2^+ [S]_{\text{SS}} - k_1^- k_2^{-*} [P]_{\text{SS}})}{k_1^{+*}[S]_{\text{SS}} + k_1^- + k_2^+ + k_2^{-*}[P]_{\text{SS}}}$$

Shannon information entropy

$$H = -\sum_{i=1}^{2} p_{\text{i}}\, ln(p_{\text{i}})$$

$$p_1 = \frac{[E]_{\text{SS}}}{[E]_{\text{tot}}}$$

$$p_2 = \frac{[ES]_{\text{SS}}}{[E]_{\text{tot}}}$$

Local stability analysis

$$\frac{d[S]}{dt} = v_{\text{in,S}} - v_1 - v_{\text{out,S}}$$

$$\frac{d[P]}{dt} = v_2 - v_{\text{out,P}}$$

$$\frac{d[E]}{dt} = -v_1 + v_2$$

$$\frac{d[ES]}{dt} = v_1 - v_2$$

$$\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$$

$$\boldsymbol{x} = (x_1, x_2)$$

$$\boldsymbol{f}(\boldsymbol{x}) = (f_1(x_1), f_2(x_2))$$

Close to steady state

$$\mathbf{J} = \begin{pmatrix} \frac{\delta f_1}{\delta x_1} & \frac{\delta f_1}{\delta x_2} \\ \frac{\delta f_2}{\delta x_1} & \frac{\delta f_1}{\delta x_2} \end{pmatrix}$$

$$v_1 = k_1^{+*}[S][E] - k_1^{-}[ES]$$

$$v_2 = k_2^{+}[ES] - k_2^{-*}[P][E]$$

Kinetic flexibility

$$\textbf{flexibilty} = \boldsymbol{Tr(J)}$$

Analysis, results and discussion

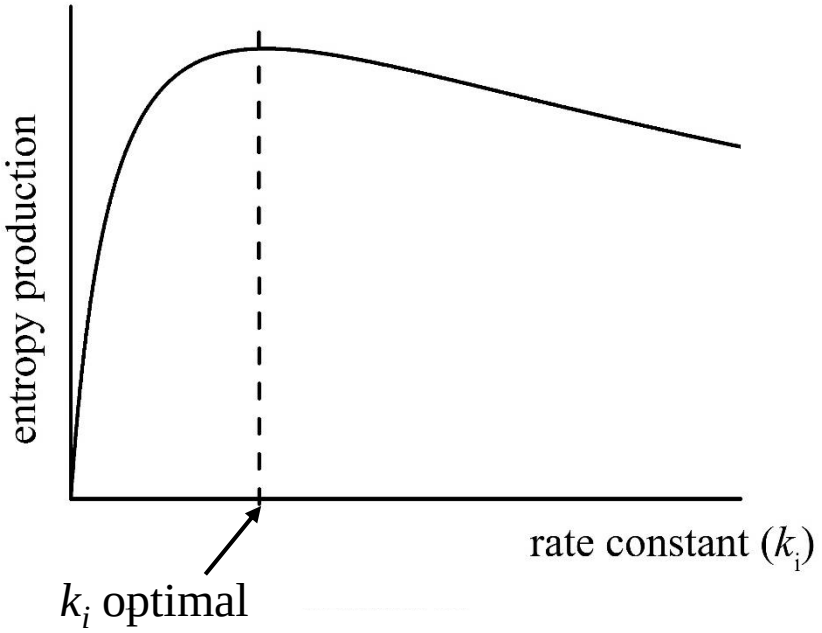
Existance of MEP

$$v = \frac{[E]_{\mathrm{tot}}(k_1^{+*}k_2^{+}[S]_{\mathrm{SS}} - k_1^{-}k_2^{-*}[P]_{\mathrm{SS}})}{k_1^{+*}[S]_{\mathrm{SS}} + k_1^{-} + k_2^{+} + k_2^{-*}[P]_{\mathrm{SS}}} \qquad K^* = \frac{k_1^{+*}k_2^{+}}{k_1^{-}k_2^{-*}} = const.$$

$$X = \text{const.} \quad v = v_{\max} \implies \sigma = \sigma_{\max}$$

Necessary optimization constraint for the existance of well-defined maximum in entropy production

$$k^{+} = k_1^{+*}k_2^{+} \qquad k^{-} = k_1^{-}k_2^{-*}$$



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Energy conservation and maximal entropy production in enzyme reactions

Andrej Dobovišek[a,b,*], Marko Vitas[e], Milan Brumen[a,b,c,d], Aleš Fajmut[a,c]

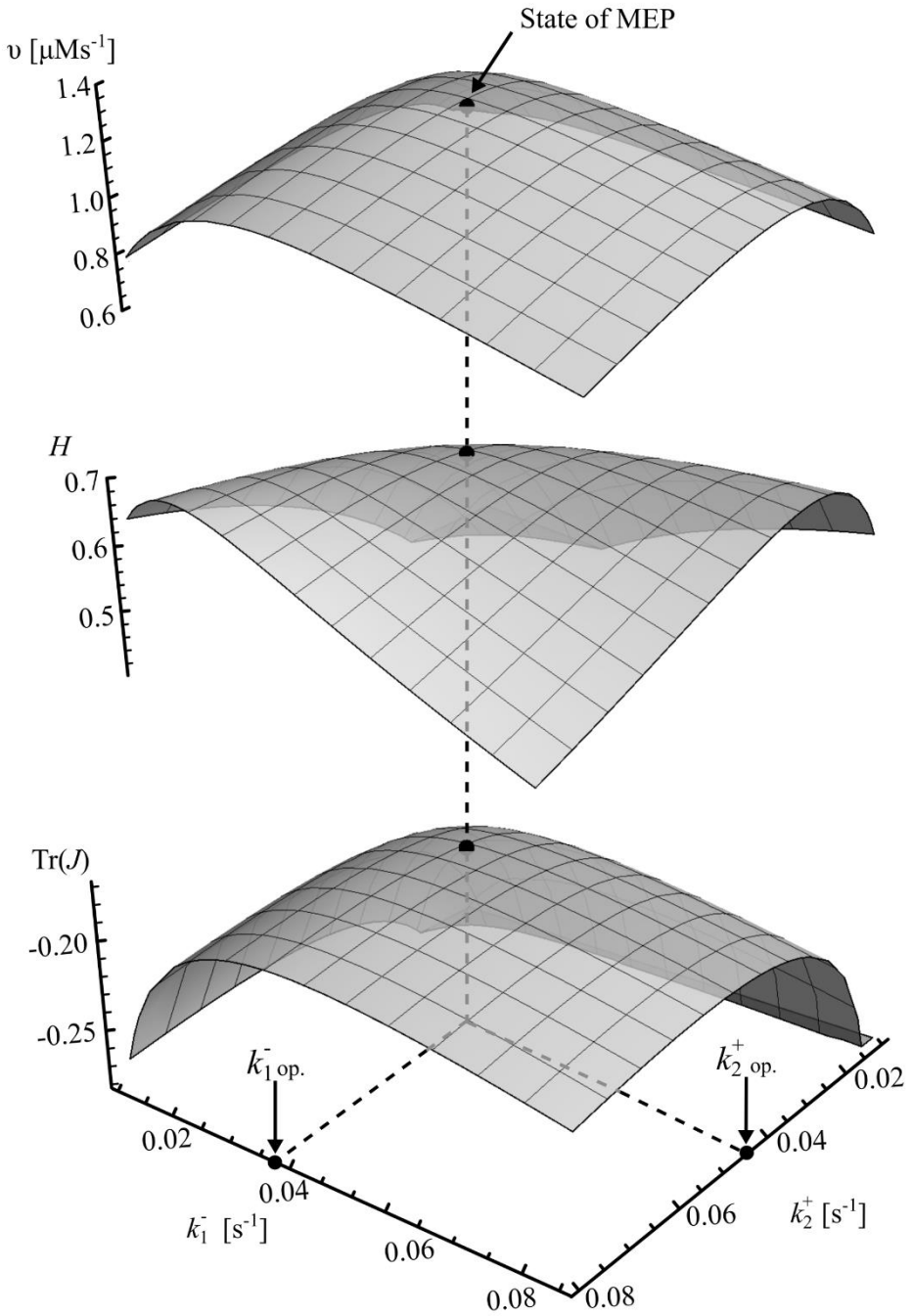
Analysis, results and discussion

Co-existance of MEP, MaxEnt and maximal flexibilty

$$v(k_2^+, k_1^-) = \frac{[E]_{\text{tot}}(k^+[S]_{ss} - k^-[P]_{ss})}{k_2^+ + \frac{k^+[S]_{ss}}{k_2^+} + k_1^- + \frac{k^-[P]_{ss}}{k_1^-}}$$

$$H(k_2^+, k_1^-) = -\frac{k_1^- + k_2^+}{k_2^+ + \frac{k^+}{k_2^+}[S]_{\text{SS}} + k_1^- + \frac{k^-}{k_1^-}[P]_{\text{SS}}} ln\left(\frac{k_1^- + k_2^+}{k_2^+ + \frac{k^+}{k_2^+}[S]_{\text{SS}} + k_1^- + \frac{k^-}{k_1^-}[P]_{\text{SS}}}\right) - \frac{\frac{k^+}{k_2^+}[S]_{\text{SS}} + \frac{k^-}{k_1^-}[P]_{\text{SS}}}{k_2^+ + \frac{k^+}{k_2^+}[S]_{\text{SS}} + k_1^- + \frac{k^-}{k_1^-}[P]_{\text{SS}}} ln\left(\frac{\frac{k^+}{k_2^+}[S]_{\text{SS}} + \frac{k^-}{k_1^-}[P]_{\text{SS}}}{k_2^+ + \frac{k^+}{k_2^+}[S]_{\text{SS}} + k_1^- + \frac{k^-}{k_1^-}[P]_{\text{SS}}}\right)$$

$$\text{Tr}(\mathbf{J})(k_2^+, k_1^-) = -\left(\frac{k^+}{k_2^+}[S]_{\text{SS}} + k_2^+ + \frac{k^-}{k_1^-}[P]_{\text{SS}} + k_1^-\right)$$



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The maximum entropy production and maximum Shannon information entropy in enzyme kinetics

Andrej Dobovišek [a,b,*], Rene Markovič [a,c,d], Milan Brumen [a,b,e,f], Aleš Fajmut [a,e]

rate constant	predicted value (MEPP)	measured value (Coverti and Del Borghi, 1998)
k_1^{+*} [$\mu M^{-1}s^{-1}$]	$3.8 \swarrow 10^{-8}$	$6.3 \swarrow 10^{-8}$
k_1^{-} [s^{-1}]	$3.6 \swarrow 10^{-2}$	$2.1 \swarrow 10^{-2}$
k_2^{+} [s^{-1}]	$4.7 \swarrow 10^{-2}$	$2.9 \swarrow 10^{-2}$
k_2^{-*} [$\mu M^{-1}s^{-1}$]	$4.7 \swarrow 10^{-8}$	$8.2 \swarrow 10^{-8}$

Results for β-lactamase enzymes

(work in progress)

β-Lactamase		$k_1^{+*}[(\mu Ms)^{-1}]$	$k_2^{+}[s^{-1}]$	$k_3^{+}[s^{-1}]$
β-Lactamase I	MEPP	47	$4.8 \cdot 10^3$	$2.7 \cdot 10^3$
	MaxEnt	47	$4.1 \cdot 10^3$	$3.2 \cdot 10^3$
	$\mathbf{Tr}(J)$	37	$3.8 \cdot 10^3$	$4.3 \cdot 10^3$
	Exp. (Christensen et al. 1991)	41±3	$(4.1 \pm 0.2) \cdot 10^3$	$(3.6 \pm 0.2) \cdot 10^3$
PC1 β-Lactamase	MEPP	24	$1.9 \cdot 10^2$	81
	MaxEnt	24	$1.5 \cdot 10^2$	97
	$\mathbf{Tr}(J)$	16	$1.3 \cdot 10^2$	171
	Exp. (Christensen et al. 1991)	22±2	$(1.7 \pm 0.1) \cdot 10^2$	96±10
RTEM β-Lactamase	MEPP	$2.1 \cdot 10^2$	$4.7 \cdot 10^3$	$0.52 \cdot 10^3$
	MaxEnt	$2.1 \cdot 10^2$	$4.2 \cdot 10^3$	$0.59 \cdot 10^3$
	$\mathbf{Tr}(J)$	$0.91 \cdot 10^2$	$2.1 \cdot 10^3$	$2.8 \cdot 10^3$
	Exp. (Christensen et al. 1991)	$(1.2 \pm 0.1) \cdot 10^2$	$(2.8 \pm 0.3) \cdot 10^3$	$(1.5 \pm 0.2) \cdot 10^3$

Results for TPI enzyme

(work in progress)

rate constant	k_1^+ [$\mu M^{-1}s^{-1}$]	k_2^+ [s^{-1}]	k_3^+ [s^{-1}]	k_4^+ [s^{-1}]	k_1^- [s^{-1}]	k_2^- [s^{-1}]	k_3^- [s^{-1}]	k_4^- [$\mu M^{-1}s^{-1}$]
Exp. (Pettersson 1992)	10	$2.0 \cdot 10^3$	$6.0 \cdot 10^4$	$0.40 \cdot 10^4$	$7.0 \cdot 10^3$	$6.0 \cdot 10^3$	$9.0 \cdot 10^4$	$0.40 \cdot 10^3$
MEPP	3	$1.9 \cdot 10^3$	$2.6 \cdot 10^4$	$3.2 \cdot 10^4$	$6.0 \cdot 10^3$	$3.0 \cdot 10^3$	$2.7 \cdot 10^4$	$3.0 \cdot 10^3$
MaxEnt	2	$2.5 \cdot 10^3$	$3.2 \cdot 10^4$	$3.0 \cdot 10^4$	$9.2 \cdot 10^3$	$2.4 \cdot 10^3$	$2.2 \cdot 10^3$	$3.1 \cdot 10^3$

In steady state with: $[S] = 3987$ μM and $[E]_{TOT} = 4$ μM

Please see poster for more details.
POSTER: Mr. Marko Šterk

Conclusions

1. We demonstrated the co-existance of well defined maxima in the density of entropy production, Shannon information entropy and kinetic flexibility with respect to enzyme rate constants for different enzymes.

2. In enzyme kinetics, the MEPP principle serves for description of statistically most probable steady states.

3. Flexible enzyme structure is closely connected with optimal thermodynamic performance of an enzyme in steady state.

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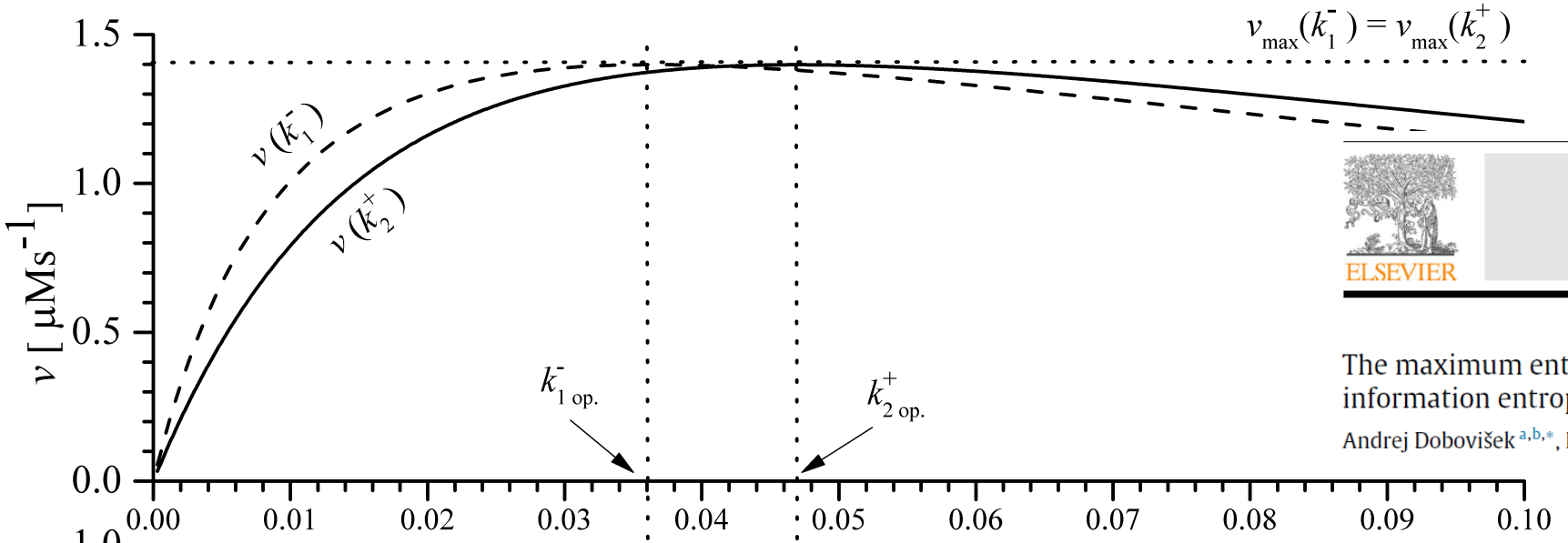

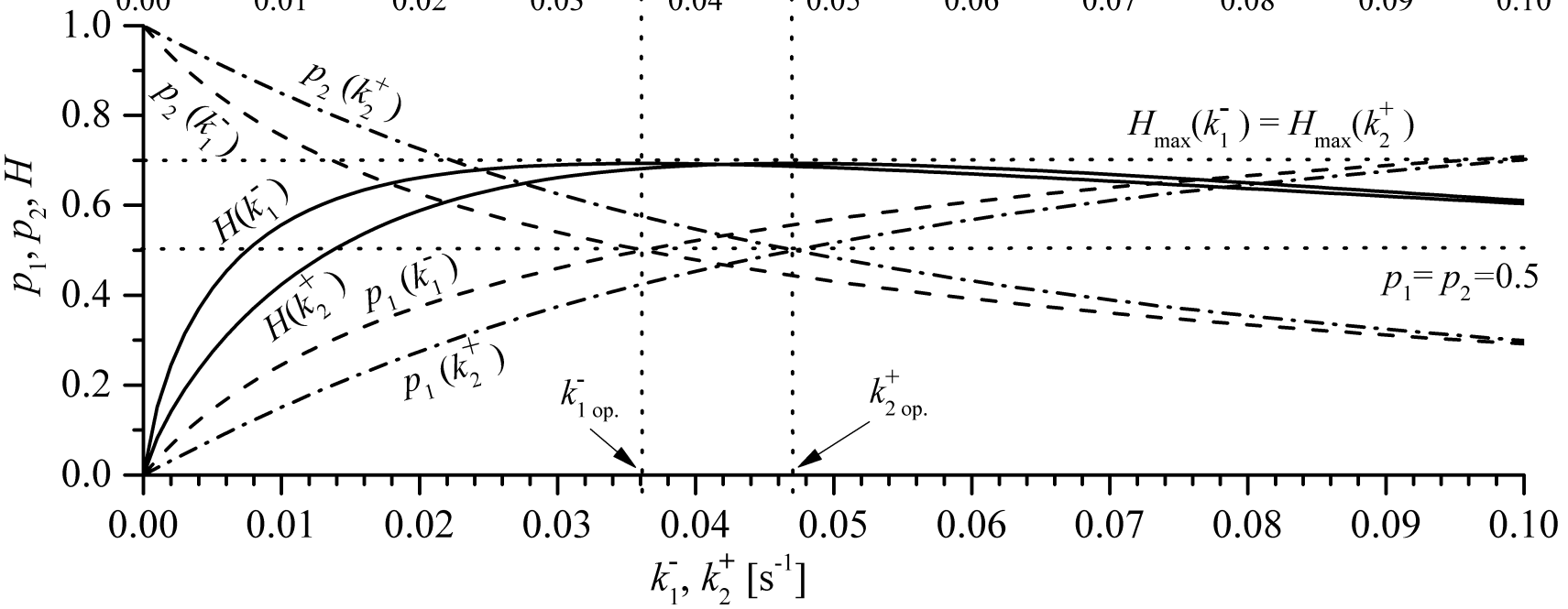

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