Michaelis-Menten kinetics

P. Palumbo **A. Borri**

National Research Council of Italy

ISTITUTO DI ANALISI DEI SISTEMI ED INFORMATICA
"Antonio Ruberti"

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

- S is the substrate
- E is the enzyme
- C is the complex SE
- P is the product

- k_{on}/k_{off} are the on/off coefficients for the complex C formation
- v is the rate for product P production
- phosphorylation/methylation, transcription, etc.

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

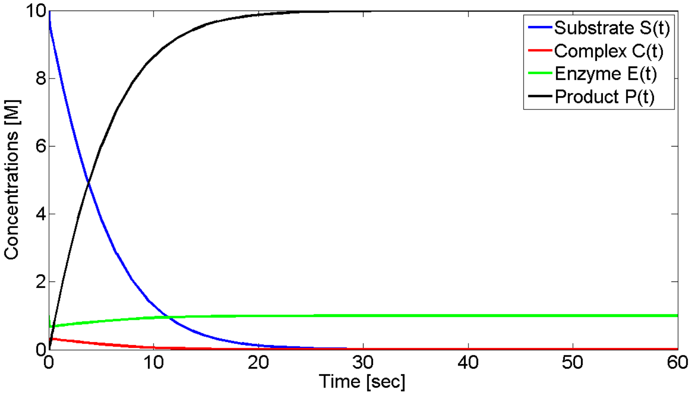
$$\begin{cases} \dot{S}(t) = -k_{on}E(t)S(t) + k_{off}C(t) & S(0) = S_{tot} \\ \dot{E}(t) = -k_{on}E(t)S(t) + k_{off}C(t) + vC(t) & E(0) = E_{tot} \\ \dot{C}(t) = k_{on}E(t)S(t) - k_{off}C(t) - vC(t) & C(0) = 0 \\ \dot{P}(t) = vC(t) & P(0) = 0 \end{cases}$$

Mass constraints

- Total substrate: $S(t) + C(t) + P(t) = S_{tot}$
- Total enzyme: $E(t) + C(t) = E_{tot}$

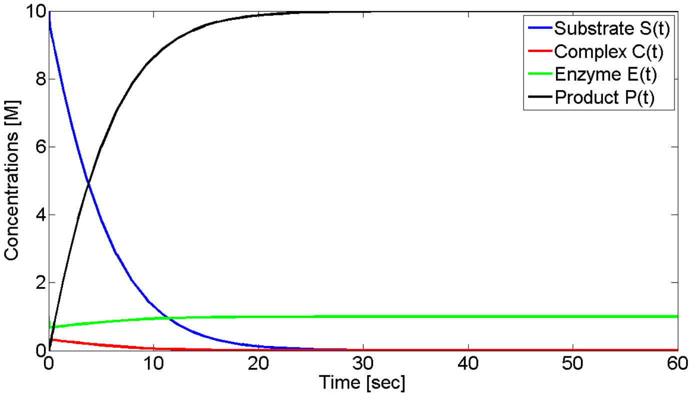
$$S + E \rightleftarrows C \rightarrow P + E$$

$$\begin{cases} \dot{S}(t) = -k_{on}\big(E_{tot} - C(t)\big)S(t) + k_{off}C(t) & S(0) = S_{tot} \\ \dot{C}(t) = k_{on}\big(E_{tot} - C(t)\big)S(t) - k_{off}C(t) - vC(t) & C(0) = 0 \end{cases}$$



Simplifying assumptions

- The complex dynamics is **faster** than the substrate dynamics
- During this fast complex transient the substrate does not decrease appreciably



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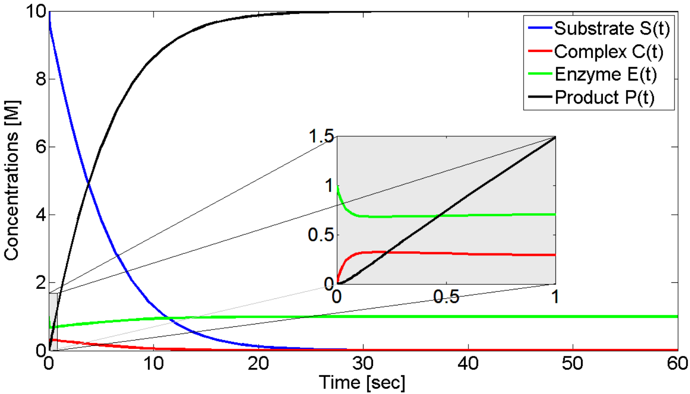

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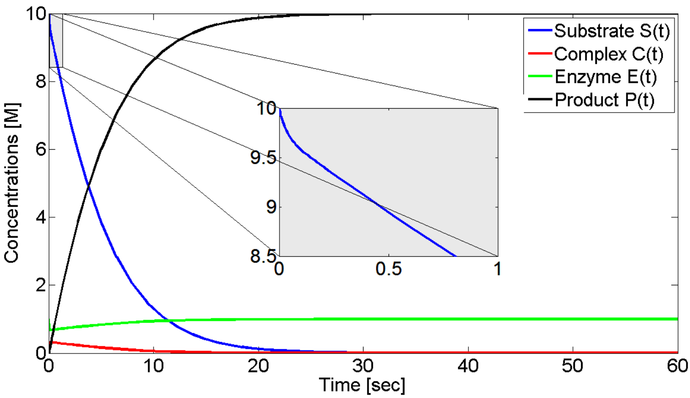
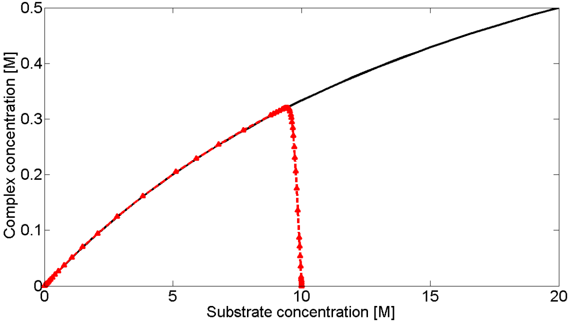


$$\dot{C}(t) = k_{on}\big(E_{tot} - C(t)\big)S(t) - k_{off}C(t) - vC(t) = 0$$

$$\Longrightarrow \qquad C(t) = E_{tot}\frac{S(t)}{S(t)+K_m} \qquad\qquad K_m = \frac{k_{off}+v}{k_{on}}$$

$$\dot{S}(t) = -vE_{tot}\frac{S(t)}{S(t)+K_m} \qquad S(0) = S_{tot}$$



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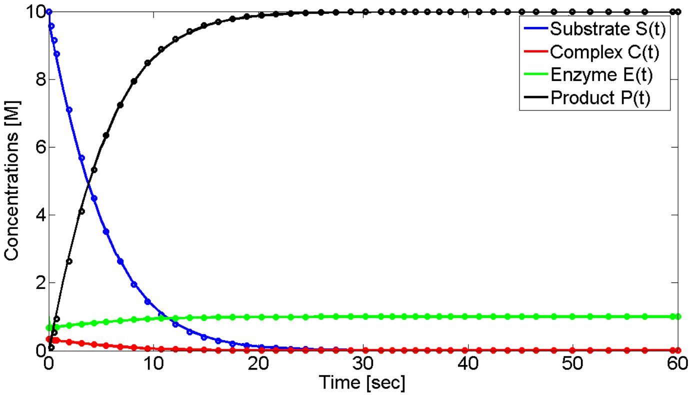
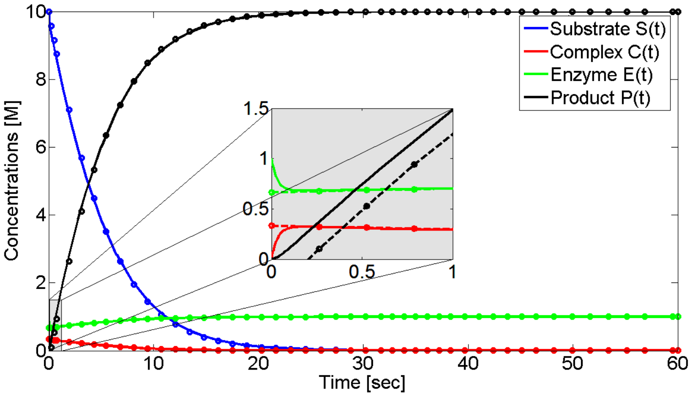


Standard Quasi Steady-State Approximation (sQSSA)

$$\dot{S}(t) = -vE_{tot}\frac{S(t)}{S(t)+K_m} \qquad S(0) = S_{tot}$$



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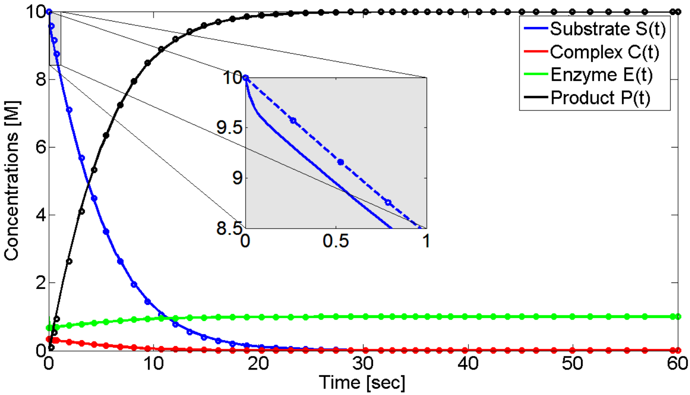


Standard Quasi Steady-State Approximation (sQSSA)

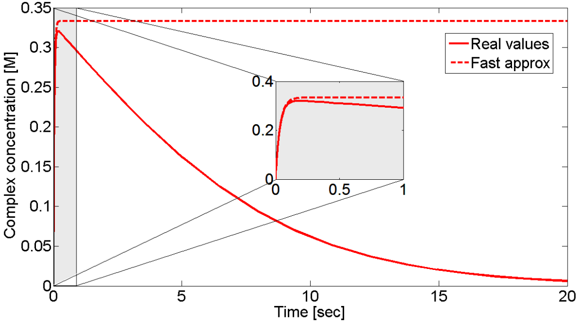
$$\dot{P}(t) = vC(t) = vE_{tot}\frac{S(t)}{S(t)+K_m} = V_{max}\frac{S(t)}{S(t)+K_m}, \qquad P(0) = 0$$

Parameters V_{max} and K_m can be computed from experiments

Fast transient: $S(t) \simeq S_{tot}$

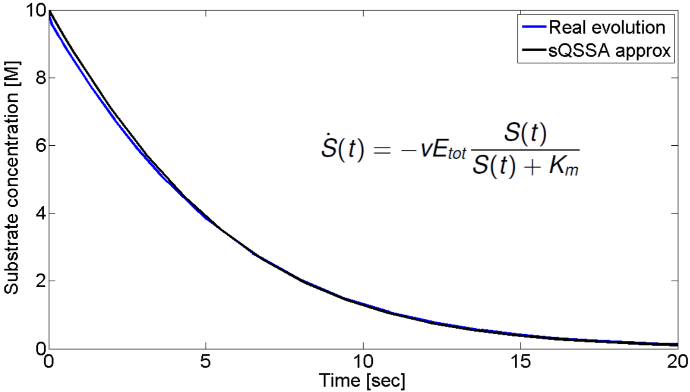
$$\dot{C}(t) \simeq k_{on}\big(E_{tot} - C(t)\big)S_{tot} - k_{off}C(t) - vC(t)$$
$$= -k_{on}\big(S_{tot} + K_m\big)C(t) + k_{on}E_{tot}S_{tot}$$

Linear dynamics: $C(t) \simeq \widetilde{C}\big(1 - exp(-t/\tau_f)\big)$ $\qquad \tau_f = \dfrac{1}{k_{on}\big(S_{tot} + K_m\big)}$



Time constant τ_s (Segel, Bull. Math. Biol. 1988)

$$\frac{\textit{total change in S after fast transient}}{\max\{|\dot{S}|\}\ \textit{after fast transient}}$$



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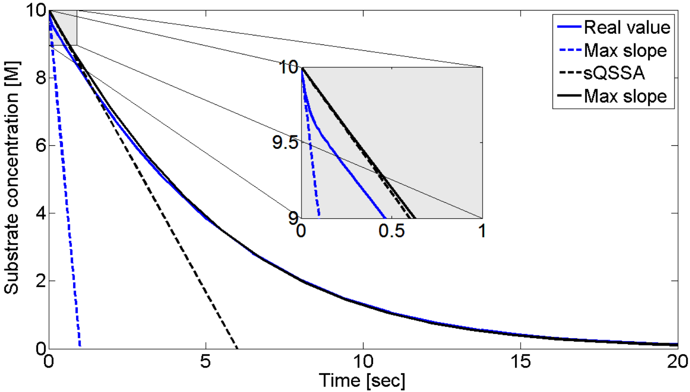


Validity of the sQSSA: computation of the time constants

Time constant τ_s (Segel, Bull. Math. Biol. 1988)

$$\frac{\textit{total change in S after fast transient}}{\max\{|\dot{S}|\}\ \textit{after fast transient}}$$

$$\tau_s = \frac{S_{tot} + K_m}{vE_{tot}}$$

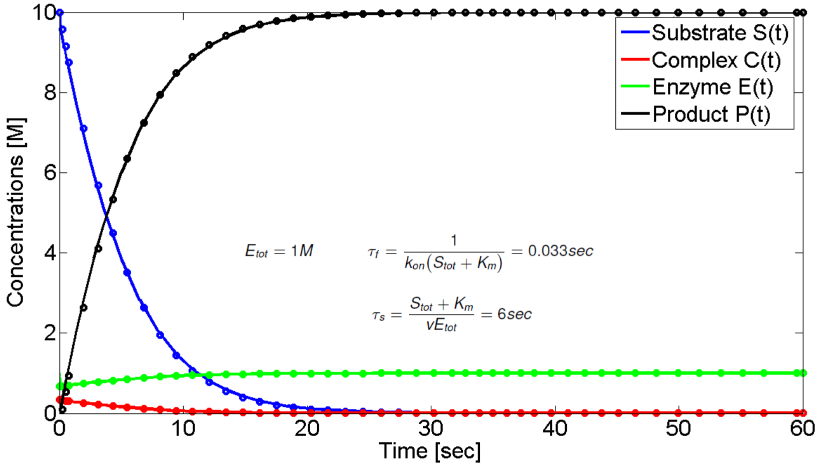
$$\tau_f \ll \tau_s \qquad \Longrightarrow \qquad \frac{E_{tot}}{S_{tot} + K_m} \ll \left(1 + \frac{k_{off}}{v}\right)\left(1 + \frac{S_{tot}}{K_m}\right)$$

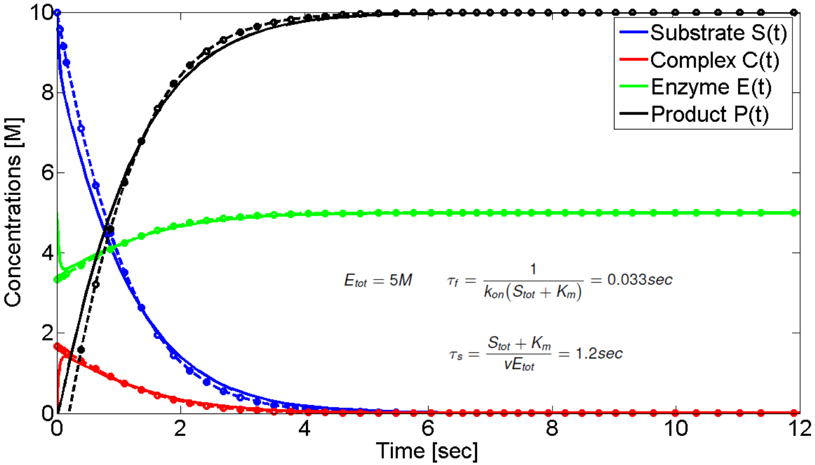
Example: $k_{on} = 1$, $k_{off} = 15$, $v = 5$, $S_{tot} = 10$, $E_{tot} = 1$, $K_m = 20$

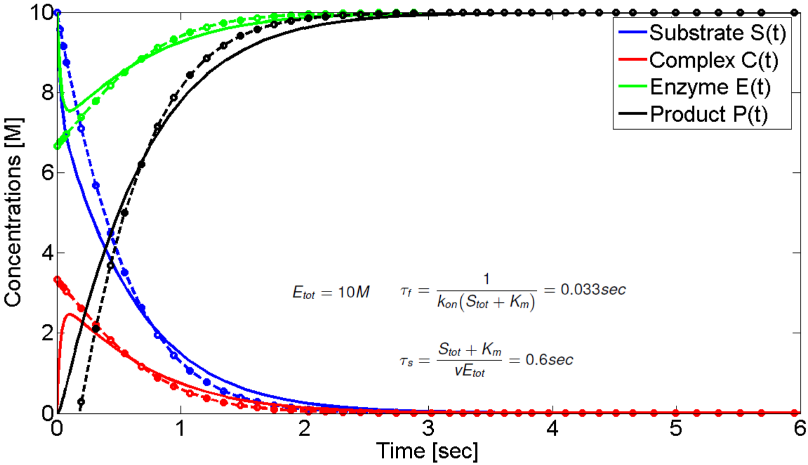
$$\tau_f = \frac{1}{k_{on}(S_{tot} + K_m)} = 0.033 sec$$

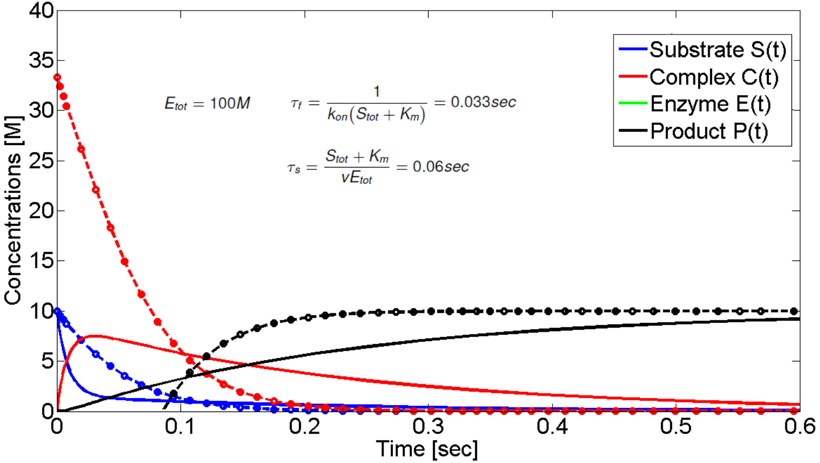
$$\tau_s = \frac{S_{tot} + K_m}{vE_{tot}} = 6 sec$$

$$\frac{E_{tot}}{S_{tot} + K_m} = 0.033 \ll 4 \cdot 1.5 = 6$$

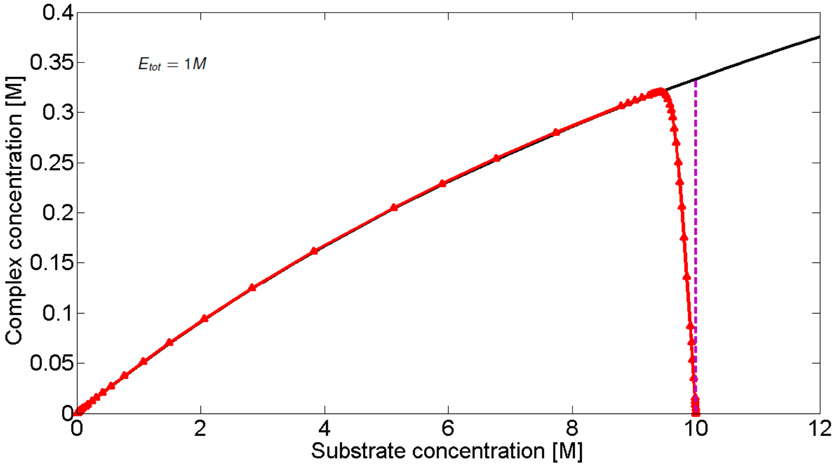

Substrate S(t)
Complex C(t)
Enzyme E(t)
Product P(t)
Concentrations [M]
Time [sec]
$E_{tot} = 1M$
$\tau_f = \frac{1}{k_{on}(S_{tot} + K_m)} = 0.033 sec$
$\tau_s = \frac{S_{tot} + K_m}{v E_{tot}} = 6 sec$


10
8
6
4
2
0
Concentrations [M]
0
2
4
6
8
10
12
Time [sec]
Substrate S(t)
Complex C(t)
Enzyme E(t)
Product P(t)
$E_{tot} = 5M$
$\tau_f = \frac{1}{k_{on}(S_{tot} + K_m)} = 0.033sec$
$\tau_s = \frac{S_{tot} + K_m}{vE_{tot}} = 1.2sec$

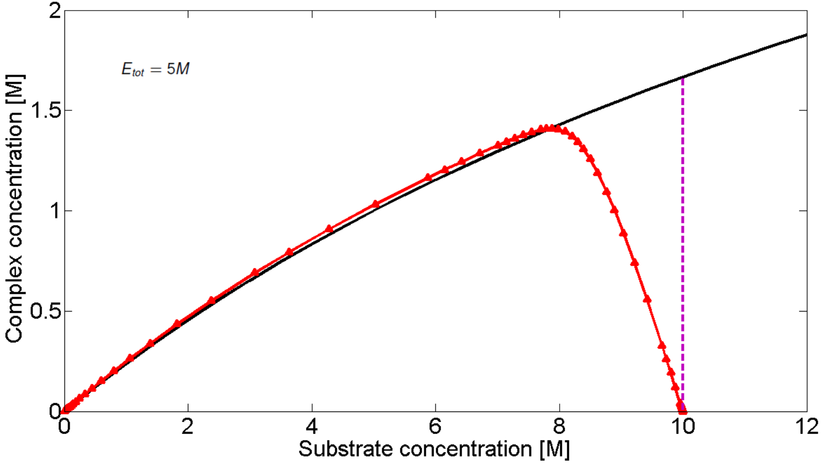

Substrate S(t)
Complex C(t)
Enzyme E(t)
Product P(t)
Concentrations [M]
Time [sec]
0
2
4
6
8
10
0
1
2
3
4
5
6
$E_{tot} = 10M$
$\tau_f = \frac{1}{k_{on}(S_{tot} + K_m)} = 0.033sec$
$\tau_s = \frac{S_{tot} + K_m}{vE_{tot}} = 0.6sec$



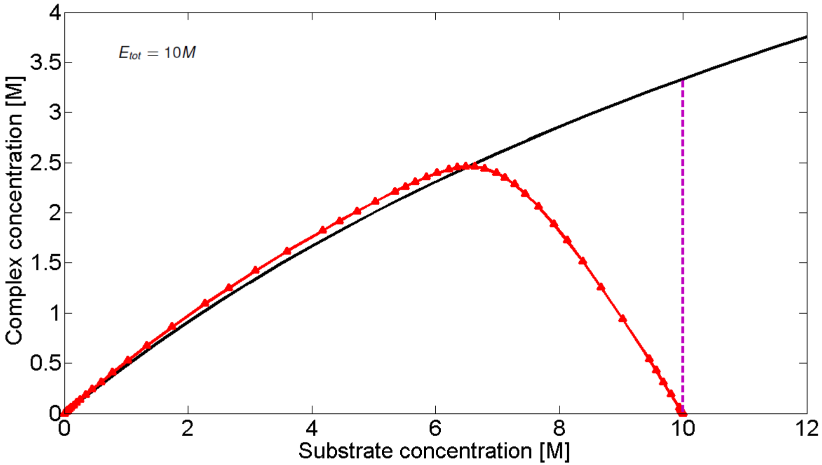
40
35
30
25
20
15
10
5
0
Concentrations [M]
0
0.1
0.2
0.3
0.4
0.5
0.6
Time [sec]
Substrate S(t)
Complex C(t)
Enzyme E(t)
Product P(t)
$E_{tot} = 100M$
$\tau_f = \frac{1}{k_{on}(S_{tot} + K_m)} = 0.033sec$
$\tau_s = \frac{S_{tot} + K_m}{vE_{tot}} = 0.06sec$


$E_{tot} = 1M$
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Complex concentration [M]
0
2
4
6
8
10
12
Substrate concentration [M]

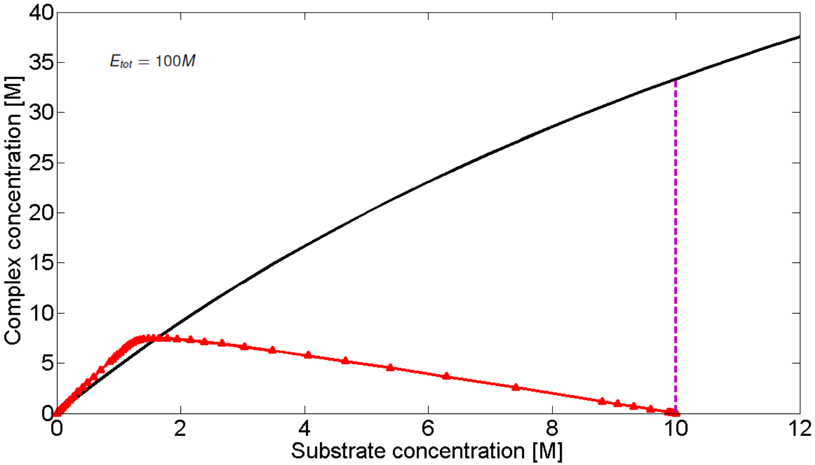
Validity of the sQSSA



Validity of the sQSSA



Validity of the sQSSA



Basic references

L.A. Segel, On the validation of the steady-state assumption of enzyme kinetics, *Bulletin of Mathematical Biology*, Vol.50, No.6, pp.589-593, 1988

Mathematical analysis of the sQSSA

J.A.M. Borghans, L.A. Segel, Extending the quasi steady-state approximation by changing variables, *Bulletin of Mathematical Biology*, Vol.58, No.1, pp.43-63, 1996

Extension of the sQSSA: the total QSSA (tQSSA)

A.R. Tzafriri, E.R. Edelman, The total quasi-steady-state approximation is valid for reversible enzyme kinetics, *Journal of Theoretical Biology*, Vol.226, pp.303-313, 2004

Extension of the tQSSA to reversible enzymatic kinetics

M.G. Pedersen, A.M. Bersani, E. Bersani, Quasi steady-state approximation in complex intraceccular signal transduction networks - a word of caution, *Journal of Mathematical Chemistry*, Vol.43, No.4, pp.1318-1344, 2007

Extension of the tQSSA to enzyme reaction cascades