Comparison of approximate kinetics for unireactant enzymes: Michaelis-Menten against the equivalent server

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BioPPN, June, 2010

Outline

Unireactant enzymatic reaction

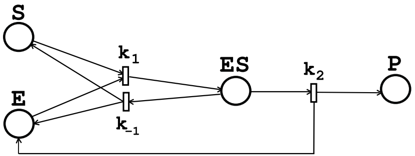
- reaction under study:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

- the enzyme, E, binds a substrate, S, in a reversible reaction
- the resulting substrate-bound enzyme, ES, gives rise to the generation of the product, P
- can me modelled either by a set of differential equations (deterministic behaviour) or by a Markov chain (stochastic behaviour)

Unireactant enzymatic reaction

- visualised in form of a Petri net:



- associated differential equations:

$$\frac{d[E]}{dt} = -k_1[E][S] + (k_{-1} + k_2)[ES]$$

$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[ES]$$

$$\frac{d[ES]}{dt} = k_1[E][S] - (k_{-1} + k_2)[ES]$$

$$\frac{d[P]}{dt} = k_2[ES]$$

Michaelis-Menten approximate kinetics

- based on the assumptions that:
  - initially we have some enzyme, $[E]_0$, and some substrate, $[S]_0$, and no complex, $[ES]_0 = 0$
  - k_2 is significantly smaller than k_1 and k_{-1}
- consequently, *ES* quickly increases up to a "plateau" level where it remains stable for a long period
- the "plateau" level can be found considering

$$\frac{d[ES]}{dt} = k_1[E][S] - [ES](k_{-1} + k_2) = 0$$

and $[E] + [ES] = [E]_0$ as

$$[ES] = \frac{[E]_0[S]}{\frac{k_{-1}+k_2}{k_1} + [S]} = \frac{[E]_0[S]}{k_M + [S]}$$

where $k_M = \frac{k_{-1}+k_2}{k_1}$ is the Michaelis-Menten constant

Michaelis-Menten approximate kinetics

- the speed of production is:

$$v_{MM} = \frac{k_2[E]_0[S]}{[S] + k_M}$$

- the resulting differential equations are:

$$\frac{d[E]}{dt} = 0$$
$$\frac{d[S]}{dt} = -\frac{k_2[E][S]}{[S] + k_M}$$
$$\frac{d[P]}{dt} = \frac{k_2[E][S]}{[S] + k_M}$$

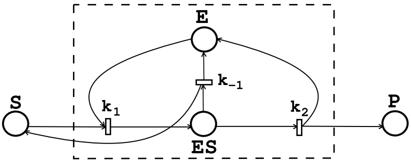
- the larger $[S]/[E]_0$ the better approximation we have

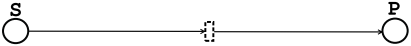
Approximate kinetics by flow equivalence

- flow equivalent server is a general technique to simplify Petri nets and other performance models
- a single transition substitutes a subnet
- requires:
  - identification of the subnet
  - identification of “input” and “output” places of the subnet
  - analysis of the subnet in isolation to determine how fast tokens are flowing from “input” places to “output” places
- analysis of the subnet is done by
  - short-circuiting the “output” and “input” places by an immediate transition
  - computing the steady state throughput of the immediate transition
- flow equivalence based substitutions give exact steady state results under strict conditions
- we use it as an approximation of the transient behaviour

Approximate kinetics by flow equivalence

- for the reactions we consider:





- S is the “input” place
- P is the “output” place
- in the short-circuited version an immediate transition is added from place P to place S

Approximate kinetics by flow equivalence

- differential equations describing the short-circuited subnet:

$$\begin{aligned}
\frac{d[E](t)}{dt} &= -k_1[E][S] + k_{-1}[ES] + k_2[ES] \\
\frac{d[S](t)}{dt} &= -k_1[E][S] + k_{-1}[ES] + k_2[ES] \\
\frac{d[ES](t)}{dt} &= +k_1[E][S] - k_{-1}[ES] - k_2[ES]
\end{aligned}$$

- mass conversation is expressed as

$$\begin{aligned}
[E] + [ES] &= \text{constant} \\
[S] + [ES] &= \text{constant}
\end{aligned}$$

- steady state is found by setting the derivatives to 0

Approximate kinetics by flow equivalence

- the resulting speed of production is:

$$v_{FES} = \frac{k_2\left([E]+[S]+k_M-\sqrt{([E]-[S])^2+2k_M([E]+[S])+k_M^2}\right)}{2}$$

- and the differential equations of the approximate solution are

$$\frac{d[E]}{dt} = 0$$

$$\frac{d[S]}{dt} = -\frac{k_2\left([E]+[S]+k_M-\sqrt{([E]-[S])^2+2k_M([E]+[S])+k_M^2}\right)}{2}$$

$$\frac{d[P]}{dt} = \frac{k_2\left([E]+[S]+k_M-\sqrt{([E]-[S])^2+2k_M([E]+[S])+k_M^2}\right)}{2}$$

Comparison of approximate kinetics

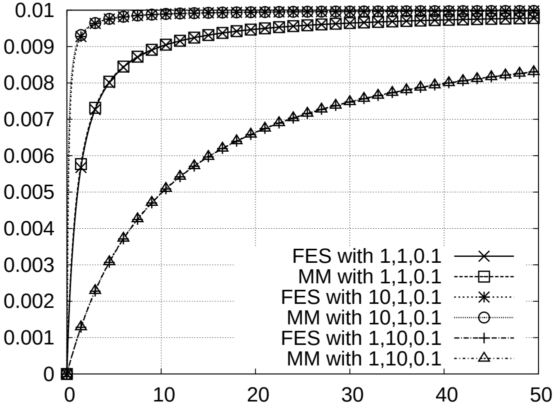
- limiting speeds of the two approximations are identical:

$$v_{\max} = \lim_{[S]\to\infty} v_{MM} = \lim_{[S]\to\infty} v_{FES} = k_2[E]$$

$$\lim_{[E]\to 0} \frac{v_{MM}}{v_{FES}} = 1$$

Comparison of approximate kinetics

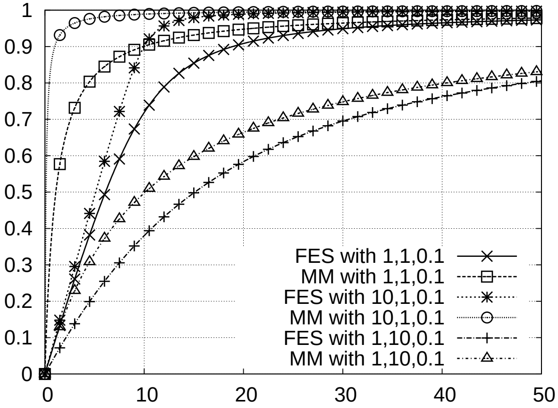
comparison of speeds with $[E] = 0.1$:



reaction rates are given in the legend in order k_1, k_{-1} and k_2

Comparison of approximate kinetics

comparison of speeds with $[E] = 10$:



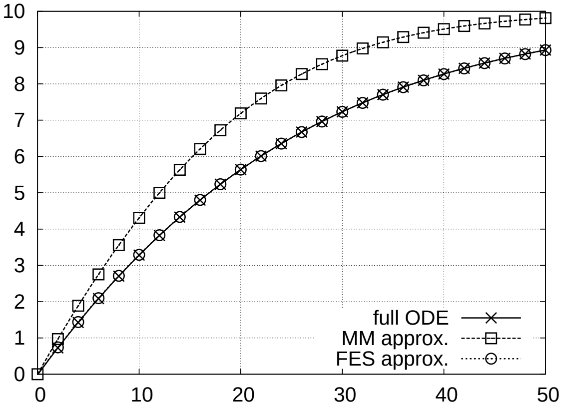
reaction rates are given in the legend in order k_1, k_{-1} and k_2

Comparison of approximate kinetics

- comparison of temporal behaviour
- three versions:
  - original set of ODE
  - MM approximation
  - FES approximation
- ODE solved by numerical integration

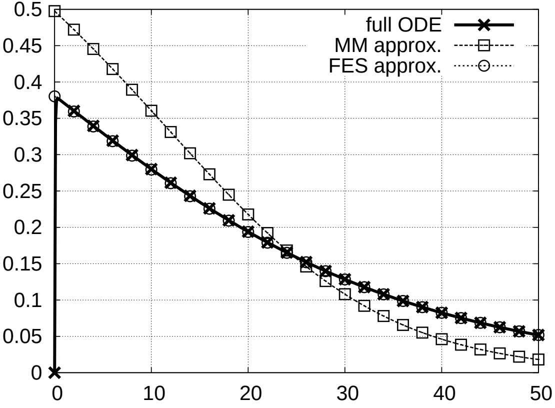
Comparison of approximate kinetics

quantity of product as function of time with $k_1 = 1$, $k_{-1} = 10$, $k_2 = 0.1$, $[E] = 10$ $[S] = 10$



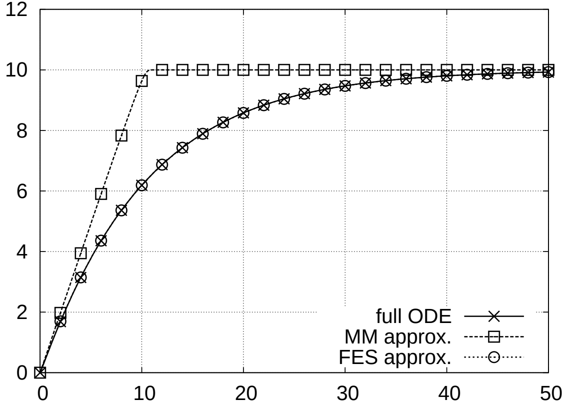
Comparison of approximate kinetics

speed of production as function of time with $k_1 = 1$, $k_{-1} = 10$, $k_2 = 0.1$, $[E] = 10$ $[S] = 10$



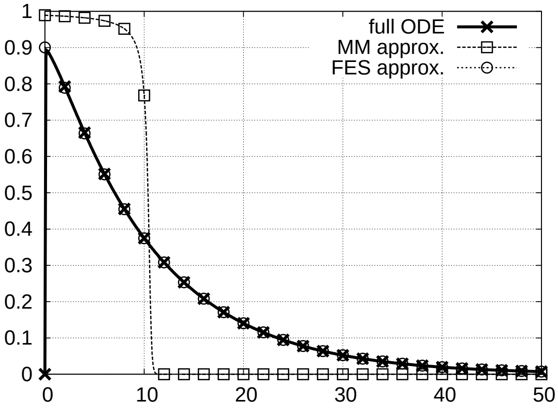
Comparison of approximate kinetics

quantity of product as function of time with $k_1 = 10$, $k_{-1} = 1$, $k_2 = 0.1$, $[E] = 10$ $[S] = 10$



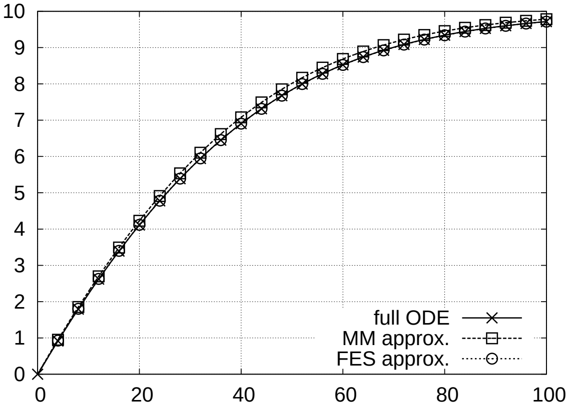
Comparison of approximate kinetics

speed of production as function of time with $k_1 = 10$, $k_{-1} = 1$, $k_2 = 0.1$, $[E] = 10$ $[S] = 10$



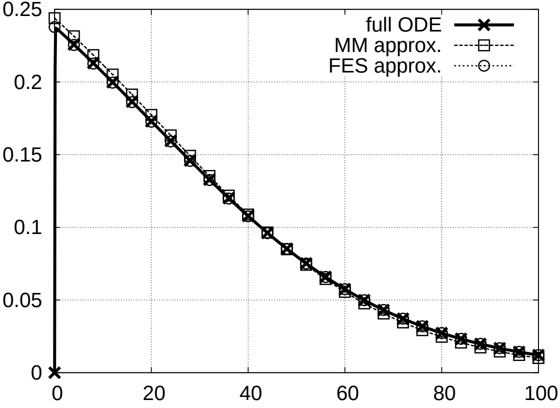
Comparison of approximate kinetics

quantity of product as function of time with $k_1 = 1$, $k_{-1} = 10$, $k_2 = 0.5$, $[E] = 1$ $[S] = 10$



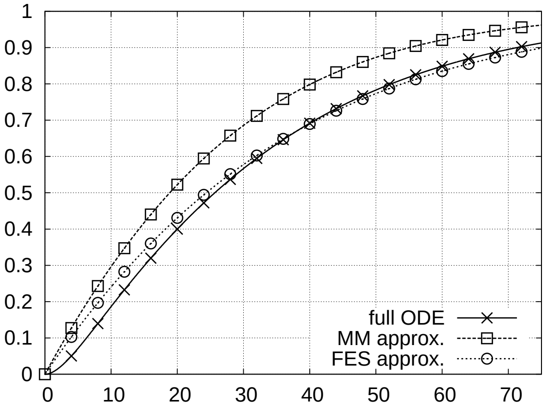
Comparison of approximate kinetics

speed of production as function of time with $k_1 = 1$, $k_{-1} = 10$, $k_2 = 0.5$, $[E] = 1$ $[S] = 10$



Comparison of approximate kinetics

quantity of product as function of time with $k_1 = 0.1$, $k_{-1} = 0.1$, $k_2 = 0.1$, $[E] = 1$ $[S] = 1$



Comparison of approximate kinetics

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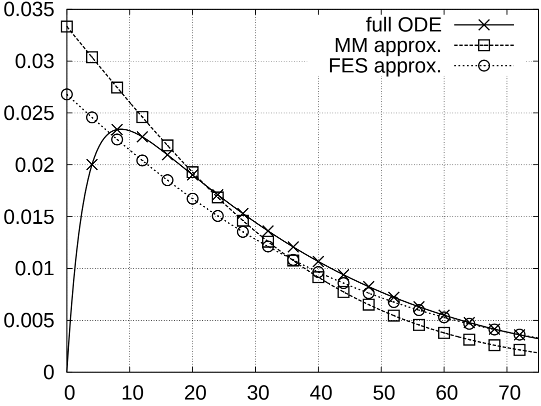
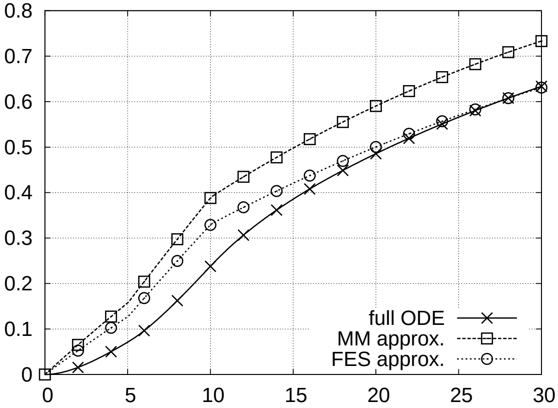


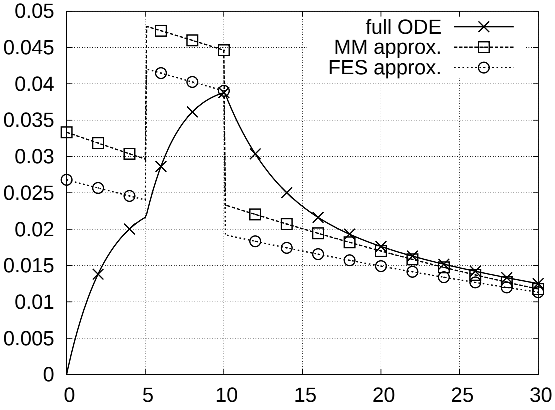
Comparison of approximate kinetics

quantity of product as function of time with $k_1 = 0.1$, $k_{-1} = 0.1$, $k_2 = 0.1$, $[E] = 1$ $[S] = 1$ and modifying substrate quantity at time 5 and 10



Comparison of approximate kinetics

speed of production as function of time with $k_1 = 0.1$, $k_{-1} = 0.1$, $k_2 = 0.1$, $[E] = 1$ $[S] = 1$ and modifying substrate quantity at time 5 and 10



Conclusion

- an alternative to the Michaelis-Menten kinetics
- based on flow equivalence
- method applicable to other small models as well
- same can be done in stochastic setting
- misses compositionality