How to derive deterministic approximations from the stochastic model of enzyme kinetics?

João Luiz de Oliveira Madeira

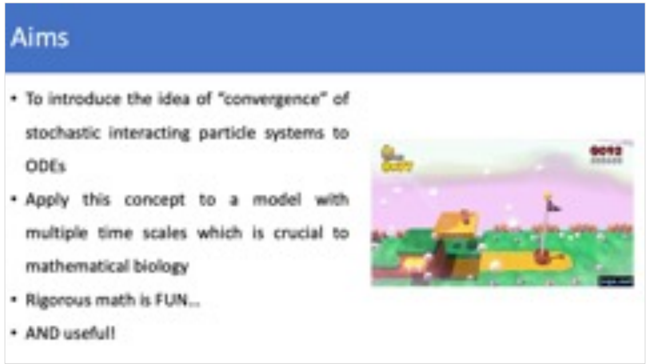
SAMBa Cohort 8

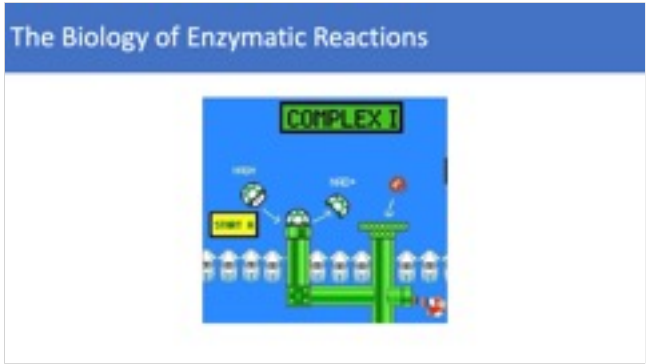
Joint work with Fernando Antonelli (Unifesp – Brazil)

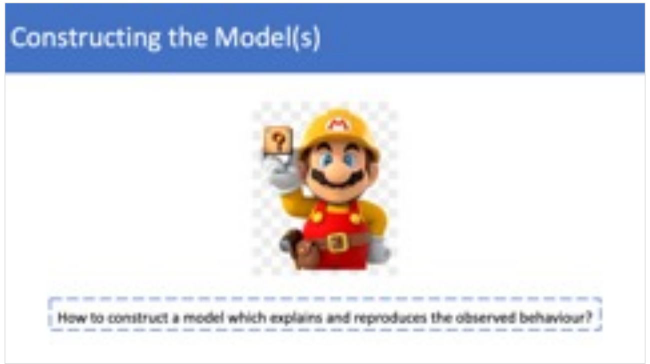
Engineering and Physical Sciences Research Council

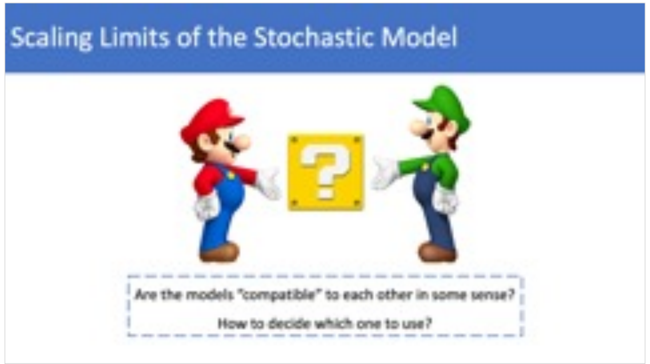
SAMBa

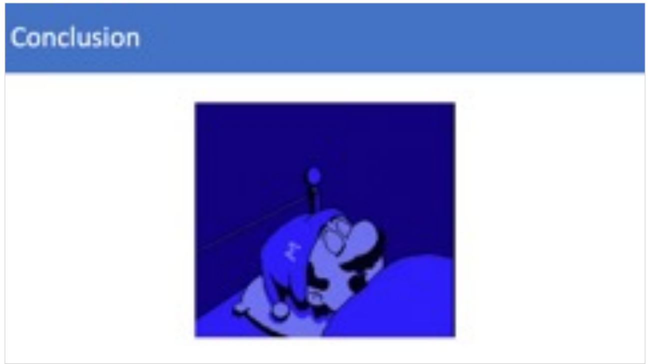
Topics


Aims
To introduce the idea of "convergence" of stochastic interacting particle systems to ODEs
Apply this concept to a model with multiple time scales which is crucial to mathematical biology
Rigorous math is FUN...
AND useful!


The Biology of Enzymatic Reactions
COMPLEX I


Constructing the Model(s)
How to construct a model which explains and reproduces the observed behaviour?

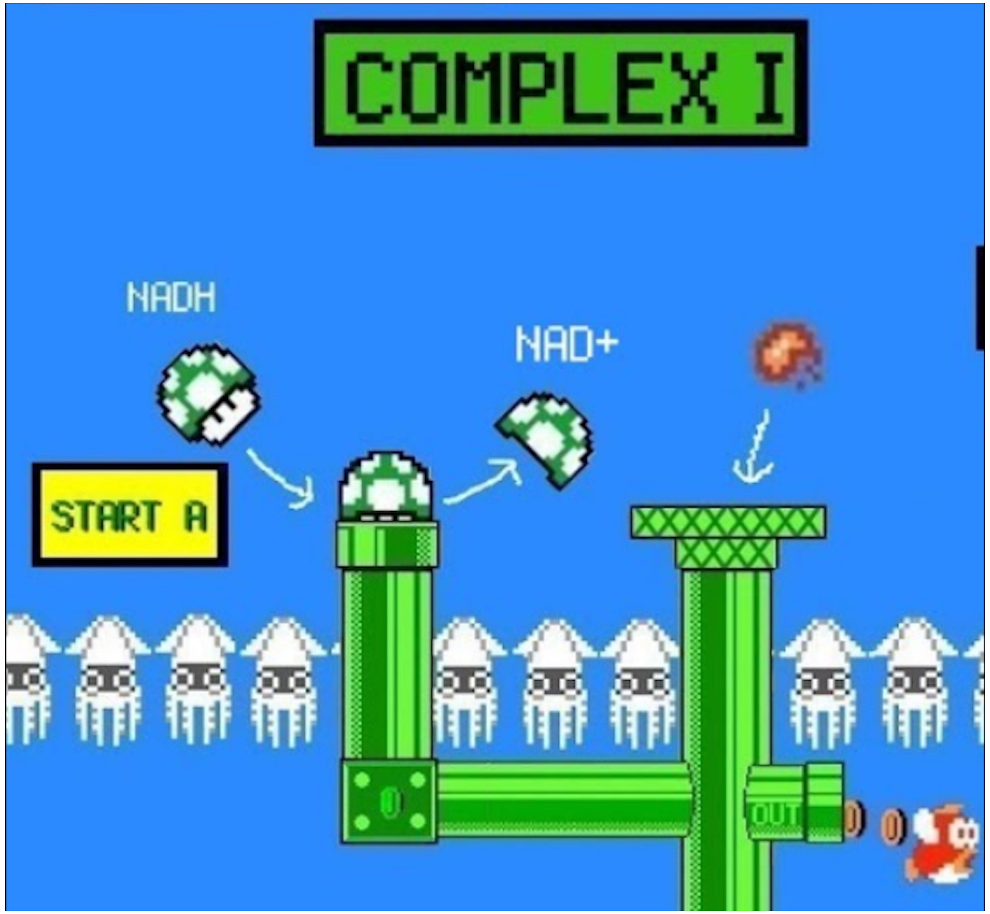

Scaling Limits of the Stochastic Model
Are the models "compatible" to each other in some sense?
How to decide which one to use?


Conclusion

Aims

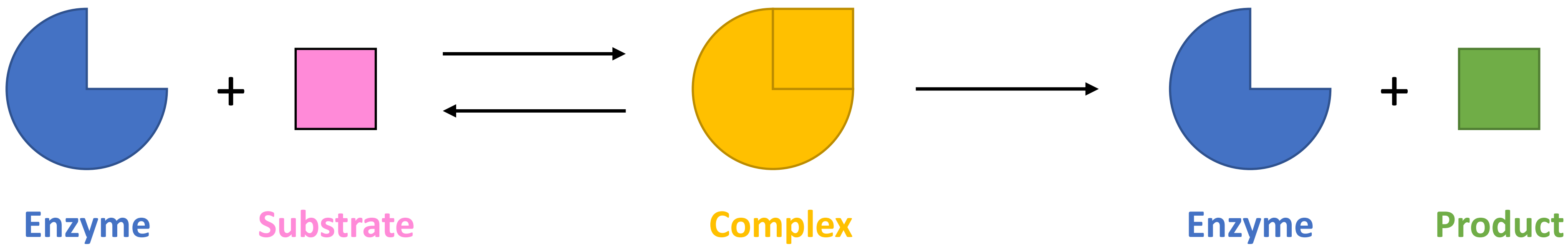
- To introduce the idea of “convergence” of stochastic interacting particle systems to ODEs
- Apply this concept to a model with multiple time scales which is crucial to mathematical biology
- Rigorous math is FUN…
- AND useful!

The Biology of Enzymatic Reactions



The Biology of Enzymatic Reactions

- Enzymes are proteins that accelerate the conversion of other molecules, but they themselves are not changed by the reaction → basic biological catalysts



- Enzymatic reactions are ubiquitous in biological systems
- Basic model in biochemical networks

(Keener 2009)

The Michaelis-Menten Kinetics

- Reaction: $S \rightarrow P$

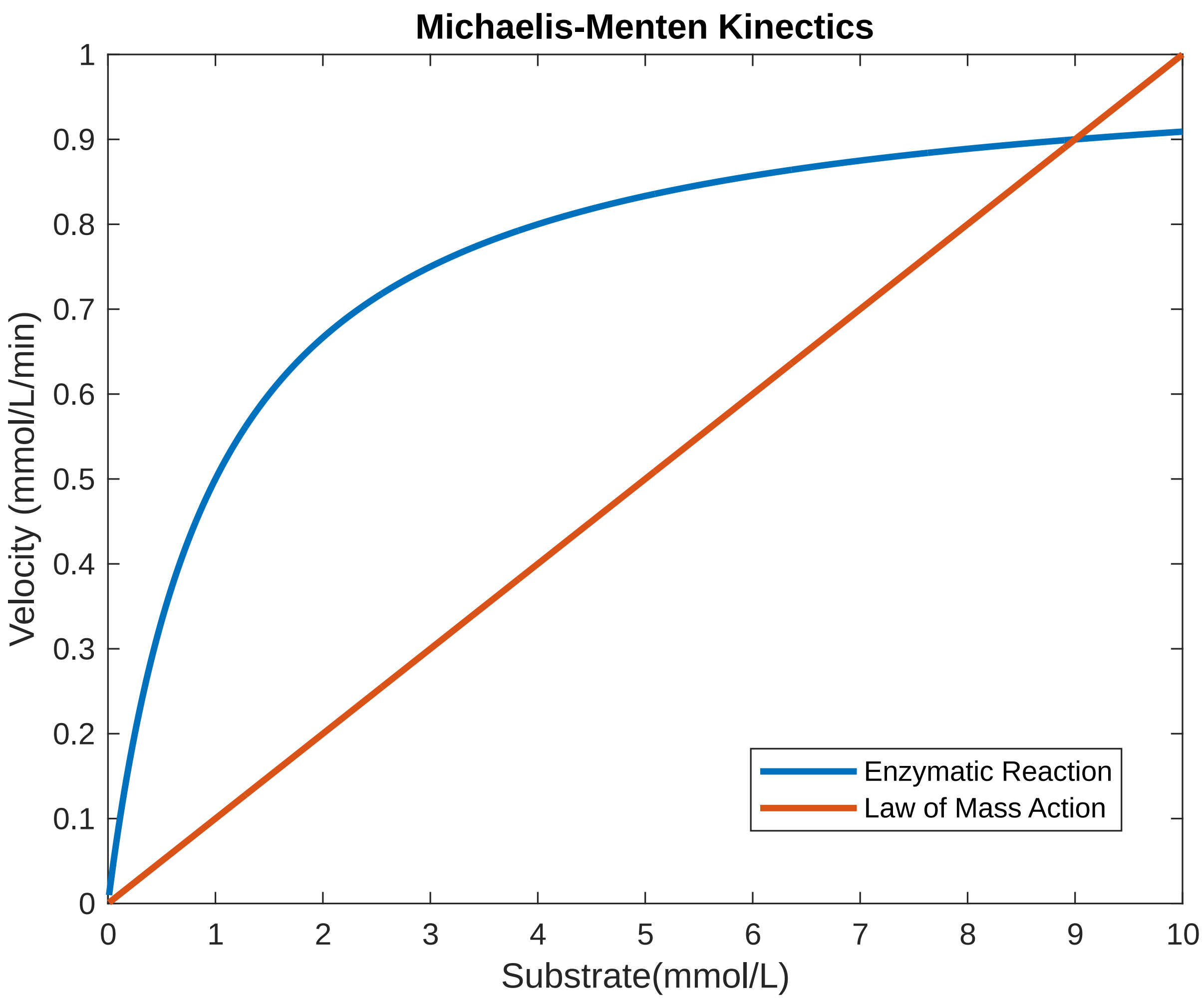
- Law of Mass Action:

$$V = k[S]$$

- The kinetics of enzymatic reactions does not follow the law of mass action

- The Michaelis-Menten Kinetics:

$$V([S]) = \frac{V_{\max} \cdot [S]}{K_M + [S]}$$



(Michaelis and Menten 1913, Keener 2009)

Constructing the Model(s)

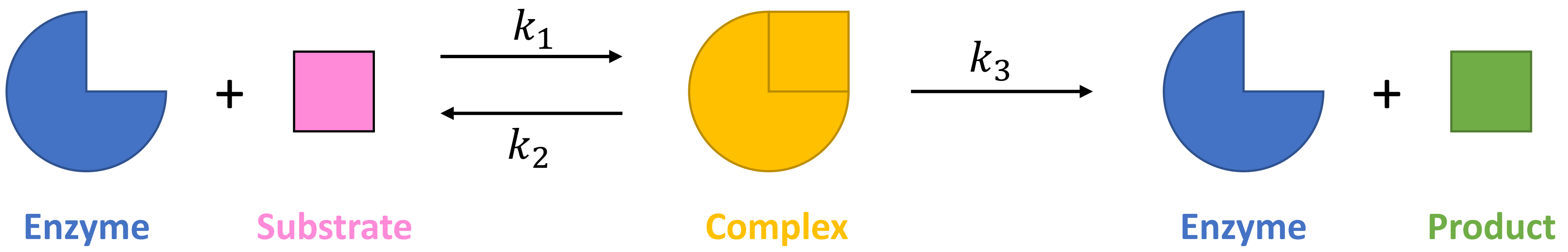
How to construct a model which explains and reproduces the observed behaviour?

Modelling

Quasi-Steady State Deterministic Approximation (QSSA)

Stochastic Interacting Particle System

Quasi-Steady State Deterministic Approximation



- Substrate ($s(t)$), product ($p(t)$), enzyme ($e(t)$) and complex ($c(t)$) are $\mathcal{C}^1$ functions from $[0, \infty)$ to $\mathbb{R}_+$

$$e(t) = e(0) - c(t)$$

$$\frac{dc}{dt}(t) = k_1 s(t) e(t) - (k_2 + k_3) c(t) \approx 0$$

$$\frac{dp}{dt}(t) = k_3 c(t) \Rightarrow \frac{dp}{dt}(t) = \frac{k_1 e(0) s(t)}{(k_2 + k_3) + s(t)} \equiv \frac{V_{max} s(t)}{K_M + s(t)}$$

$$\frac{ds}{dt}(t) = -k_1 s(t) e(t) + k_2 c(t) = -\frac{k_1 e(0) s(t)}{(k_2 + k_3) + s(t)}$$

(Briggs and Haldane 1925)

The QSSA Approach

Advantages

1. Good fit to the data (when a large number of substrate molecules is considered)
2. Simple, but a meaningful, explanation

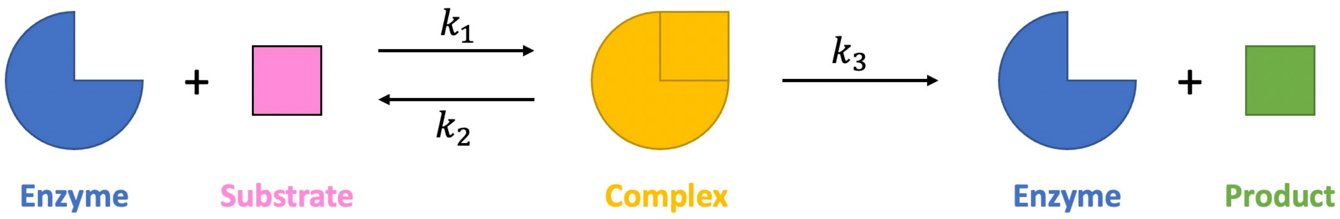
Disadvantages

1. It is difficult to make the argument rigorous

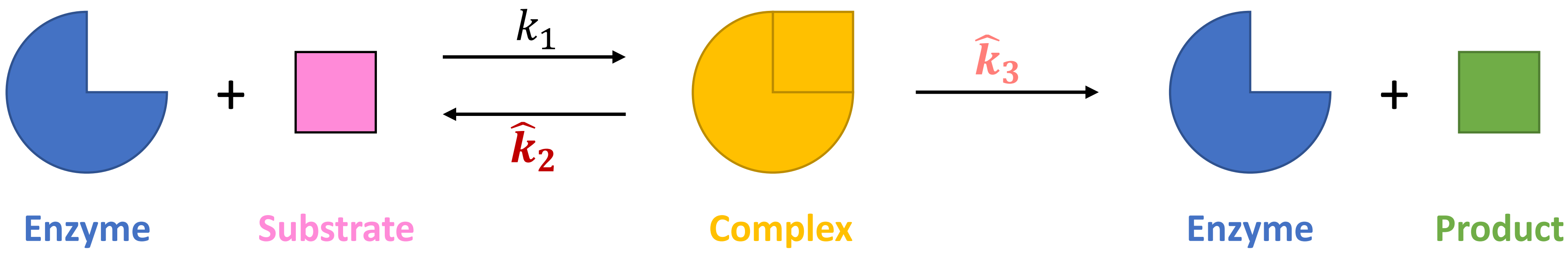
$$\frac{dc}{dt}(t) = k_1 s(t) e(t) - (k_2 + k_3) c(t) \approx 0$$

$$e(t) = e(0) - c(t)$$

2. It does not fit the data well for low number of molecules



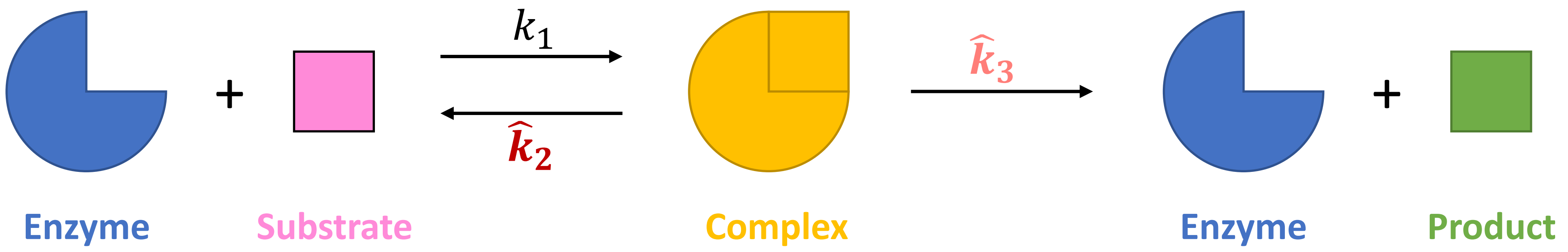
Stochastic Interacting Particle System



- We model our system as a continuous-time Markov chain
- Let $N \in \mathbb{N}$ be a scaling parameter
- $(X^N(t))_{t\geq 0} = (X_1^N(t), X_2^N(t), X_3^N(t), X_4^N(t))_{t\geq 0}$ which is a jump process in $(\mathbb{N}_0)^4$:
  - $X_1^N(0) = Ns_0$ and $X_2^N(0) = Np_0$
  - For all $t \geq 0$, $X_3^N(t) + X_4^N(t) \equiv m > 0$
  - $\hat{k}_2 = Nk_2$ and $\hat{k}_3 = Nk_3$

(Darden 1979)

Stochastic Interacting Particle System



- Given a state $(\xi_1, \xi_2, \xi_3, \xi_4) \in (\mathbb{N}_0)^4$:

$$(\xi_1, \xi_2, \xi_3, \xi_4) \to (\xi_1 - 1, \xi_2, \xi_3 - 1, \xi_4 + 1) \text{ with rate } k_1 \xi_1 \xi_3$$

$$(\xi_1, \xi_2, \xi_3, \xi_4) \to (\xi_1 + 1, \xi_2, \xi_3 + 1, \xi_4 - 1) \text{ with rate } \mathrm{N} k_2 \xi_4$$

$$(\xi_1, \xi_2, \xi_3, \xi_4) \to (\xi_1, \xi_2 + 1, \xi_3 + 1, \xi_4 - 1) \text{ with rate } \mathrm{N} k_3 \xi_4$$

(Darden 1979)

The Stochastic Interacting Particle System Approach

Advantages

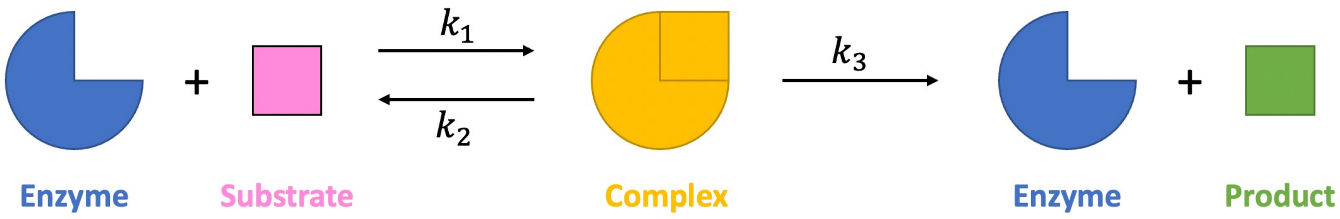
Disadvantages

Advantages

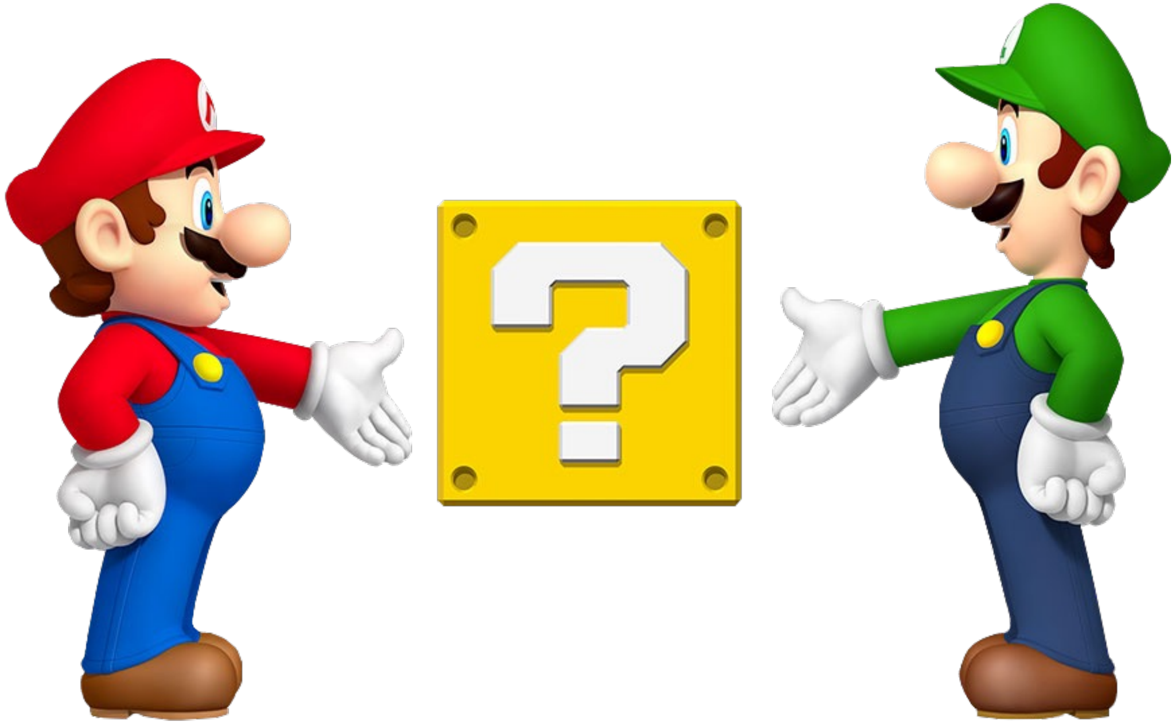
1. Good fit to the data
2. The description of the model is simple and precise, and it does not require any approximation

Disadvantages

1. It is difficult to analyse



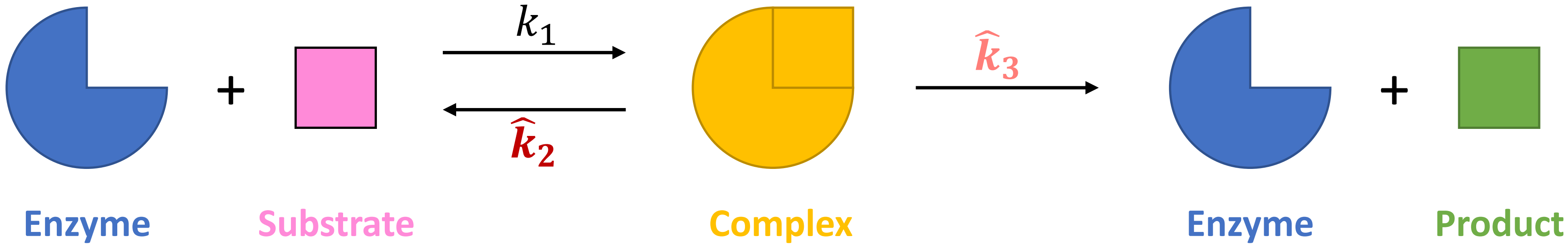
Scaling Limits of the Stochastic Model



Are the models “compatible” to each other in some sense?

How to decide which one to use?

The Scaling Limit



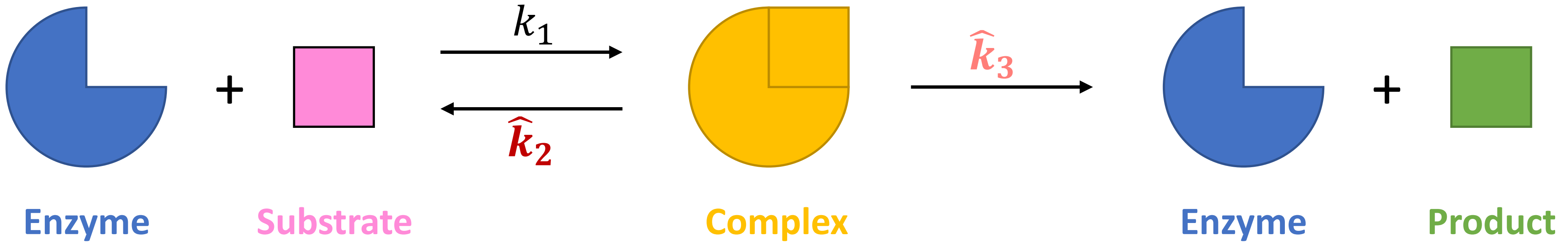
- Let $N \in \mathbb{N}$ be a scaling parameter
- $(X^N(t))_{t\geq 0} = (X_1^N(t), X_2^N(t), X_3^N(t), X_4^N(t))_{t\geq 0}$ which is a jump process in $(\mathbb{N}_0)^4$:
  - $X_1^N(0) = Ns_0$ and $X_2^N(0) = Np_0$
  - For all $t \geq 0$, $X_3^N(t) + X_4^N(t) \equiv m > 0$
  - $\hat{k}_2 = Nk_2$ and $\hat{k}_3 = Nk_3$

$$x_1^N(t) \equiv \frac{X_1^N(t)}{N} \text{ and } x_2^N(t) \equiv \frac{X_2^N(t)}{N}$$

$$f(X^N(t)) \equiv \left(x^N(t)\right) = (x_1^N(t), x_2^N(t))$$

(Darden 1979)

The Scaling Limit



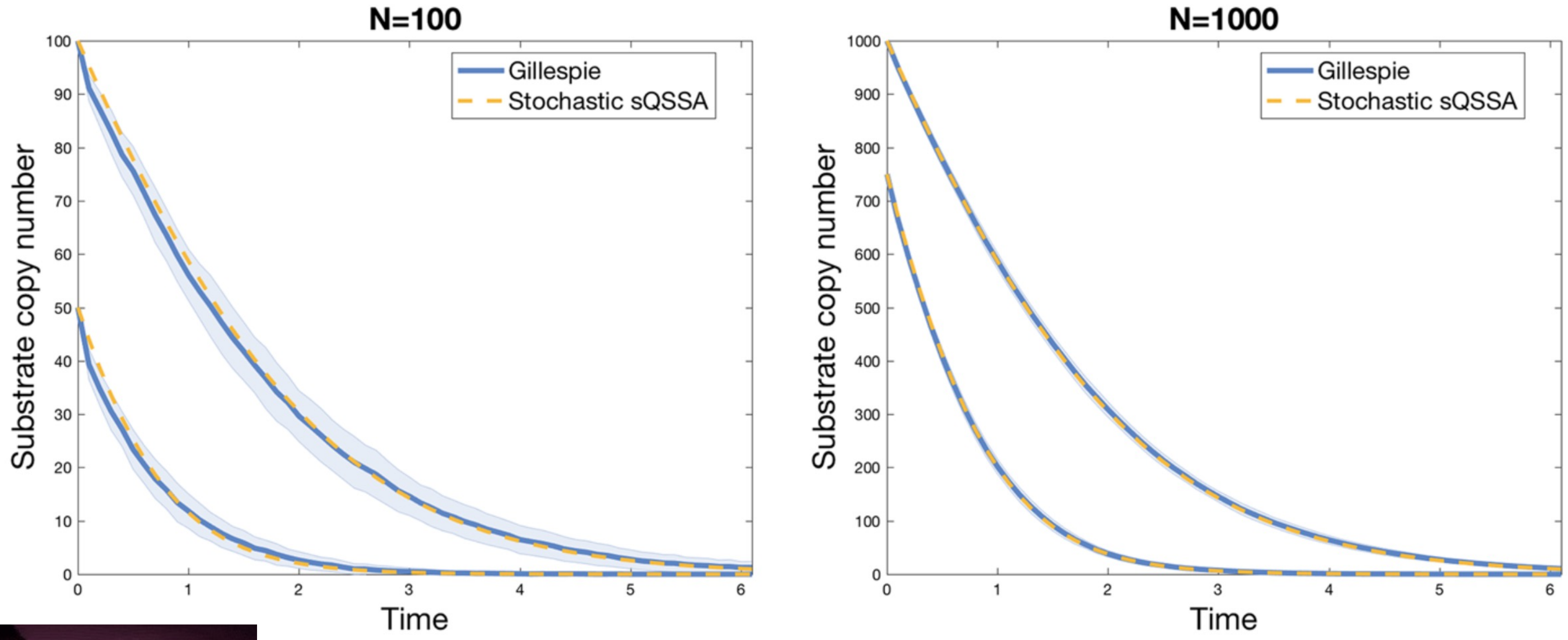
- Given a state $(\zeta_1, \zeta_2, \xi_3, \xi_4) = \left(\frac{\xi_1}{N}, \frac{\xi_2}{N}, \xi_3, \xi_4\right) \in (\mathbb{R}_+)^4$:

$$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1 - \frac{1}{N}, \zeta_2, \xi_3 - 1, \xi_4 + 1\right) \text{ with rate } \mathrm{N} k_1 \zeta_1 \xi_3$$

$$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1 + \frac{1}{N}, \zeta_2, \xi_3 + 1, \xi_4 - 1\right) \text{ with rate } \mathrm{N} k_2 \xi_4$$

$$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1, \zeta_2 + \frac{1}{N}, \xi_3 + 1, \xi_4 - 1\right) \text{ with rate } \mathrm{N} k_3 \xi_4$$

“Empirical” Evidence of Convergence



How to define *convergence*?

(Kang et al. 2019)

Weak Convergence of Probability Measures

- Let (E, d) be a complete and separable metric space
- Let $(\mu_N)_{N\in\mathbb{N}}$ be a sequence of Borel probability measures on E
- Consider a sequence of random variables $(X_N)_{N\in\mathbb{N}}$, each of them taking values on E, such that the law of X_N is given by μ_N
- Consider a random variable X, also taking values on E, with associated law μ
- **Definition:** We say $(X_N)_{N\in\mathbb{N}}$ converges weakly to X if for any bounded and continuous function $f: E \to \mathbb{R}$:

$$\lim_{n\to\infty} \mathbb{E}_{\mu_N}[f(X_N)] = \mathbb{E}_{\mu}[f(X)]$$

Weak Convergence in the Space of Càdlàg Functions

QSSA model →

$$\begin{cases} \frac{ds}{dt}(t) = -\frac{k_1 e(0) s(t)}{(k_2+k_3)+s(t)} \\ \frac{dp}{dt}(t) = \frac{k_1 e(0) s(t)}{(k_2+k_3)+s(t)} \\ s(0) = s_0 \text{ and } p(0) = p_0 \end{cases}$$

Markov Chain → $(X^N(t))_{t\geq 0} = (X_1^N(t), X_2^N(t), X_3^N(t), X_4^N(t))_{t\geq 0}$

- Fix $T > 0$
- For each $\mathrm{N} \in \mathbb{N}$, consider the random variable $x_N = \left(x_N(t)\right)_{0\leq t\leq T} = \left(\frac{X_1^N(t)}{N}, \frac{X_2^N(t)}{N}\right)_{0\leq t\leq T}$
- Our limiting "random" variable is the unique solution to the ODE $x = \left(s(t), p(t)\right)_{0\leq t\leq T}$
- We consider E as the space of **càdlàg** functions from $[0, \mathrm{T}]$ to $\mathbb{R}^2$: $\mathcal{D}([0,T], \mathbb{R}^2)$
- We say a function is **càdlàg** if it is right-continuous with left limits

Weak Convergence in the Space of Càdlàg Functions

- We can define a topology in $\mathcal{D}([0,T],\mathbb{R}^2)$ which is called the **Skorokhod** topology

- The usual strategy to prove convergence is:

  1. To show that any subsequence of $(\mu_N)_{N\in\mathbb{N}}$ has a weakly convergent subsequence

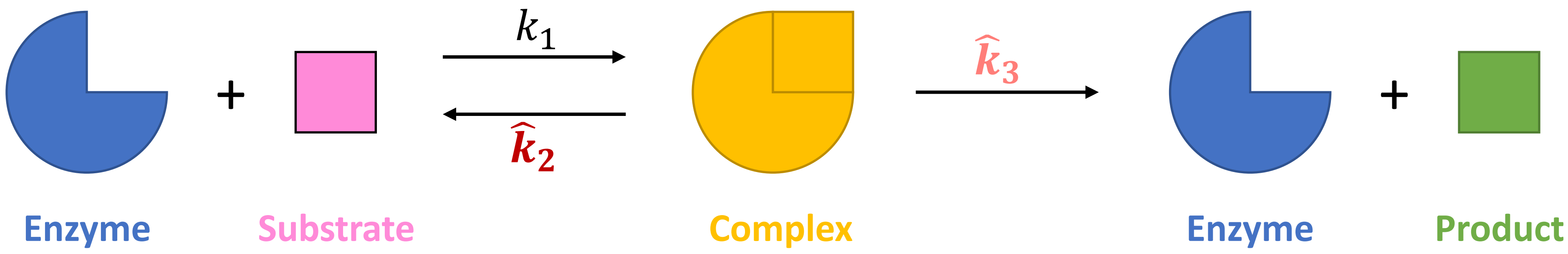
  2. To prove that every subsequential limit has the same law (or is the same càdlàg function)

- The study of this approach is beyond the scope of this talk

- To prove that $(f(X^N(t)))_{0\le t\le T} = \left(\frac{X_1^N(t)}{N}, \frac{X_2^N(t)}{N}\right)_{0\le t\le T} \Rightarrow \big(x(t)\big)_{0\le t\le T} = \big(s(t), p(t)\big)_{0\le t\le T}$, it is enough to prove that, for $\forall \epsilon > 0$:

$$\lim_{N\to\infty} \mathbb{P}\left[\left\{\sup_{0\le t\le T} \big|\big|x_N(t) - x(t)\big|\big|_\infty > \epsilon\right\}\right] = 0$$

Computing the "action" of the Generator on the Slow Variables

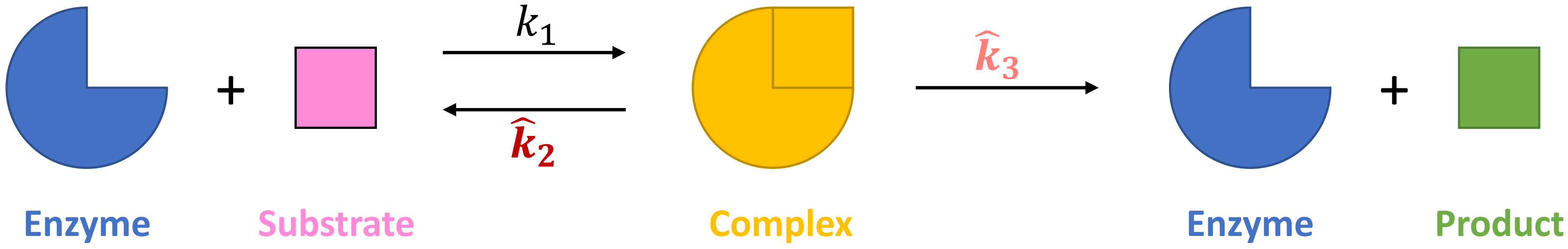


- Given a state $(\zeta_1, \zeta_2, \xi_3, \xi_4) = \left(\frac{\xi_1}{N}, \frac{\xi_2}{N}, \xi_3, \xi_4\right) \in (\mathbb{R}_+)^4$, we compute the impact of the dynamics on f:

Transition	Rate	Difference
$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1 - \frac{1}{N}, \zeta_2, \xi_3 - 1, \xi_4 + 1\right)$	$\mathrm{N} k_1 \zeta_1 \xi_3$	$\left(-\frac{1}{N}, 0\right)$
$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1 + \frac{1}{N}, \zeta_2, \xi_3 + 1, \xi_4 - 1\right)$	$\mathrm{N} k_2 \xi_4$	$\left(+\frac{1}{N}, 0\right)$
$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1, \zeta_2 + \frac{1}{N}, \xi_3 + 1, \xi_4 - 1\right)$	$\mathrm{N} k_3 \xi_4$	$\left(0, +\frac{1}{N}\right)$

Drift Vector: $\gamma_f(\xi_1, \xi_2, \xi_3, \xi_4) = (-k_1 \zeta_1 \xi_3 + k_2 \xi_4, k_3 \xi_4)$

The Martingale Problem



- We can describe the dynamics of the process $(f(X^N(t)))_{0\le t\le T} = \left(\frac{X_1^N(t)}{N}, \frac{X_2^N(t)}{N}\right)_{0\le t\le T}$ by:

$$f\left(X^N(t)\right) = f\left(X^N(0)\right) + M^N(t) + \int_0^t \gamma_f\left(X^N(\tau)\right)d\tau \longrightarrow \text{Stochastic Process}$$

- The process $\left(M_N(t)\right)_{t\ge 0}$ indicates the fluctuations of the system, and it is a martingale

(Very) Brief Review of Martingales - I

- Consider a probability space $(\Omega, \mathcal{F}, \mathbb{P})$
- A filtration $(\mathcal{F}_t)_{t\geq 0}$ of $\mathcal{F}$ can be thought as a family of σ-algebras indexed by time such that s $\leq t \Rightarrow \mathcal{F}_s \subseteq \mathcal{F}_t$
- For a more practical point of view, we can think about $\mathcal{F}_t$ as the σ-algebra generated by the events that happened until time t
- A **Martingale** $\left(M(t)\right)_{t\geq 0}$ is a process such that:
  - ✓ $M(t)$ is $\mathcal{F}_t$-measurable and $\mathbb{E}[|M(t)|] < \infty, \forall t \geq 0$
  - ✓ $\mathbb{E}[M(t)|\mathcal{F}_s] = M(s), \forall 0 \leq s \leq t$
- **Intuition:** the amount of money a player wins in a fair game, Brownian motion

(Very) Brief Review of Martingales – II

- There are really nice estimates regarding martingales

- A particular case of the optional stopping theorem says that:

$$\mathbb{E}[M(t)] = \mathbb{E}[M(0)], \forall t \geq 0$$

- For example, Doob's L2 Inequality shows that:

$$\mathbb{E}\left[\sup_{0\leq t\leq T} ||M^N(t)||_2\right] \lesssim \mathbb{E}\left[||M^N(t)||_2^2\right]$$

An Exponential Martingale Estimate

- It is possible to construct an exponential martingale based on our Markov process and verify that (see Darling and Norris 2008):

Lemma: For $\epsilon > 0$ sufficiently small, for all $N \in \mathbb{N}$, we have:

$$\mathbb{P}\left[\left\{\sup_{0\le t\le T} \left|\left|M^N(t)\right|\right|_\infty \ge \epsilon\right\}\right] \le 4\exp\left(-\frac{\epsilon^2}{2A_f T}\right),$$

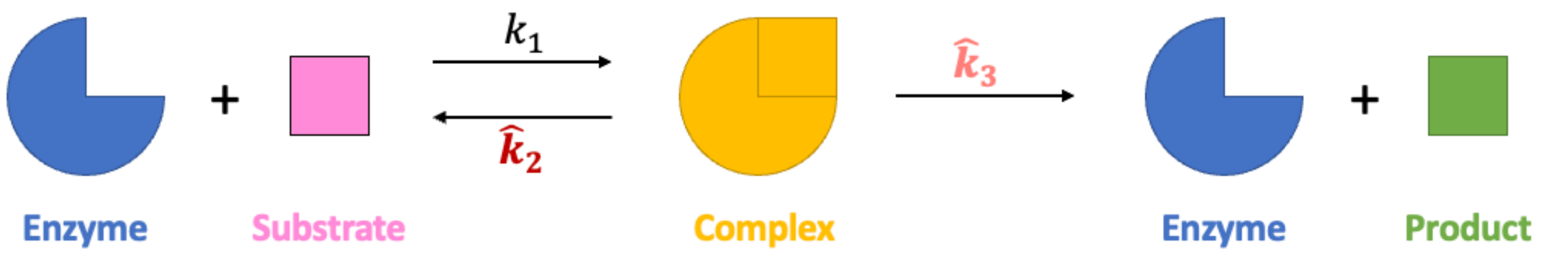
where:

$$A_f = \frac{em\left(k_1\left(s_0 + \frac{m}{N}\right) + (k_2 \vee k_3)\right)}{N}.$$

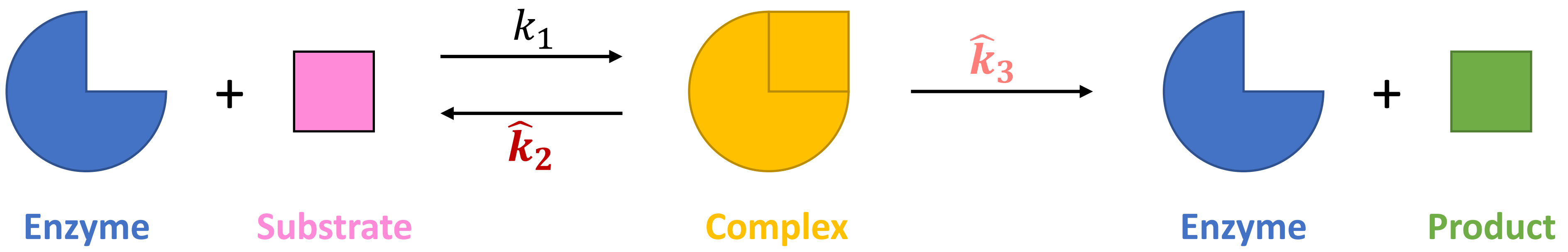
$X_1^N(0) = Ns_0$ and $X_2^N(0) = Np_0$

For all $t \ge 0$, $X_3^N(t) + X_4^N(t) \equiv m > 0$

$\hat{k}_2 = Nk_2$ and $\hat{k}_3 = Nk_3$



Rewriting our Problem



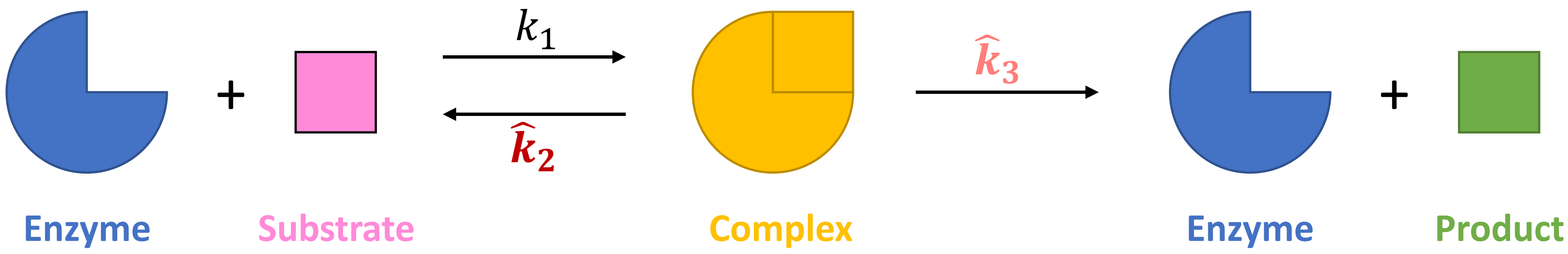
$$f\left(X^N(t)\right) = f\left(X^N(0)\right) + M^N(t) + \int_0^t \gamma_f\left(X^N(\tau)\right)d\tau$$ → Stochastic Process

$$\left(s(t), p(t)\right) = (s_0, p_0) + \int_0^t b(s(\tau), p(\tau))d\tau$$ → ODE

$$b(s(\tau), p(\tau)) = \left(-\frac{mk_3 s(\tau)}{\frac{k_2 + k_3}{k_1} + s(\tau)}, \frac{mk_3 s(\tau)}{\frac{k_2 + k_3}{k_1} + s(\tau)}\right)$$

$$\gamma_f\left(X^N(\tau)\right) = \left(-k_1 \frac{X_1^N(\tau)}{N} X_3^N(\tau) + k_2 X_4^N(\tau), k_3 X_4^N(\tau)\right)$$

The Problem of the Fast Variables



- Given a state $(\zeta_1, \zeta_2, \xi_3, \xi_4) = \left(\frac{\xi_1}{N}, \frac{\xi_2}{N}, \xi_3, \xi_4\right) \in (\mathbb{R}_+)^4$:

$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1 - \frac{1}{N}, \zeta_2, \xi_3 - 1, \xi_4 + 1\right)$ with rate $\mathrm{N}k_1\zeta_1\xi_3$

$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1 + \frac{1}{N}, \zeta_2, \xi_3 + 1, \xi_4 - 1\right)$ with rate $\mathrm{N}k_2\xi_4$

$(\zeta_1, \zeta_2, \xi_3, \xi_4) \to \left(\zeta_1, \zeta_2 + \frac{1}{N}, \xi_3 + 1, \xi_4 - 1\right)$ with rate $\mathrm{N}k_3\xi_4$

The number of molecules of enzyme and complex oscillates too fast when $N \to \infty$

↓

No convergence can occur

↓

We still can make some nice estimates about the integral of the path

Dealing with the Fast variables

- We now consider the process $\left(g\left(X^N(t)\right)\right)_{t\geq 0}$, given by $g\left(X^N(t)\right) = \left(\frac{X_3^N(t)}{N}, \frac{X_4^N(t)}{N}\right)$

- The drift vector is now $\gamma_g\left(X^N(t)\right) = \left(-k_1 \frac{X_1^N(t)}{N} X_3^N(t) + X_4^N(t)(k_2 + k_3), k_1 \frac{X_1^N(t)}{N} X_3^N(t) - X_4^N(t)(k_2 + k_3)\right)$

- We can again write a martingale $\left(L^N(t)\right)_{t\geq 0}$ associated to g:

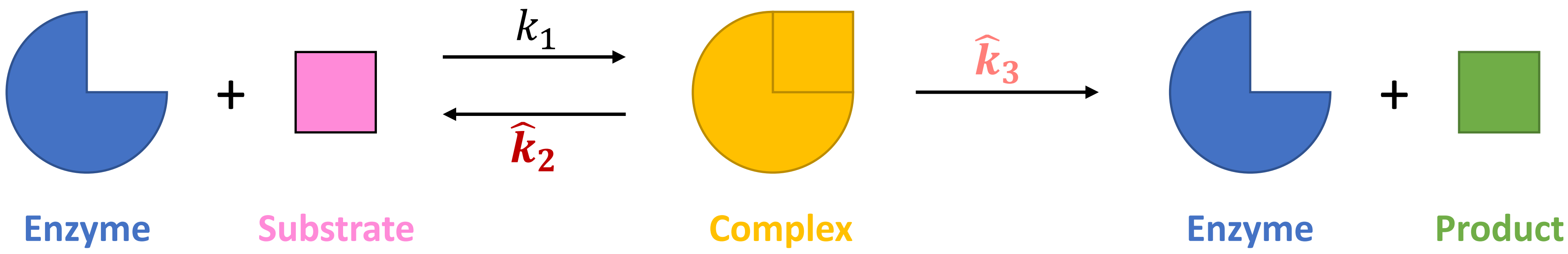
$$g\left(X^N(t)\right) = g\left(X^N(0)\right) + L^N(t) + \int_0^t \gamma_g\left(X^N(\tau)\right) d\tau$$

$$\sup_{0\leq t\leq T} \left|\left|\int_0^t \gamma_g\left(X^N(\tau)\right) d\tau\right|\right|_\infty \leq \frac{m}{N} + \sup_{0\leq t\leq T} \left|\left|L^N(t)\right|\right|$$

$$A_g = \frac{em\left(k_1\left(s_0 + \frac{m}{N}\right) + (k_2 + k_3)\right)}{N}.$$

$$\mathbb{P}\left[\left\{\sup_{0\leq t\leq T} \left|\left|L^N(t)\right|\right|_\infty \geq \epsilon\right\}\right] \leq 4\exp\left(-\frac{\epsilon^2}{2A_g T}\right)$$

Finishing this (Finally)



$$f\left(X^N(t)\right) = f\left(X^N(0)\right) + M^N(t) + \int_0^t \gamma_f\left(X^N(\tau)\right)d\tau$$ → Stochastic Process

$$\left(s(t), p(t)\right) = (s_0, p_0) + \int_0^t b(s(\tau), p(\tau))d\tau$$ → ODE

$$b(s(\tau), p(\tau)) = \left(-\frac{m k_3 s(\tau)}{\frac{k_2 + k_3}{k_1} + s(\tau)}, \frac{m k_3 s(\tau)}{\frac{k_2 + k_3}{k_1} + s(\tau)}\right)$$

$$\gamma_f\left(X^N(\tau)\right) = \left(-k_1 \frac{X_1^N(\tau)}{N} X_3^N(\tau) + k_2 X_4^N(\tau), k_3 X_4^N(\tau)\right)$$

Aim: To apply Gronwall's lemma

$$f(t) \le C + D\int_0^t f(s)ds, \quad \forall 0 \le t \le T \Rightarrow f(T) \le Ce^{DT}$$

Finishing this (Finally)

$$\sup_{0\le\tau\le t}\left|\left|f\left(X^N(\tau)\right)-\left(s(\tau),p(\tau)\right)\right|\right|_\infty \le \left|\left|f\left(X^N(0)\right)-(s_0,p_0)\right|\right|_\infty + \sup_{0\le\tau\le t}\left|\left|M^N(\tau)\right|\right|_\infty$$

$$+\frac{k_1k_3m}{k_2+k_3}\int_0^t \sup_{0\le r\le\tau}\left|\left|f(X^N(r))-\left(s(r),p(r)\right)\right|\right|_\infty d\tau$$

$$+\sup_{0\le\tau\le t}\left|\left|\int_0^\tau \frac{(k_1s(r)+k_2)}{(k_1s(r)+k_2+k_3)}\gamma_g\left(X^N(r)\right)dr\right|\right|_\infty$$

Monotonic function

Second Mean Value Theorem for Integrals: Let $h, w\colon [0,T] \to \mathbb{R}$ such that h is monotonic and w is Lebesgue integrable. Then there exists c ∈ $[0,T]$ such that

$$\int_0^T h(t)w(t)dt = h(0+)\int_0^T w(t)dt + h(T-)\int_0^T w(t)dt$$

The Final Theorem (Finally)

Theorem: For the initial conditions, $X_1^N(0) = Ns_0$ and $X_2^N(0) = Np_0$

For all $t \geq 0$, $X_3^N(t) + X_4^N(t) \equiv m > 0$

$\widehat{k}_2 = Nk_2$ and $\widehat{k}_3 = Nk_3$

and taking $f\left(X^N(t)\right) = \left(\frac{X_1^N(t)}{N}, \frac{X_2^N(t)}{N}\right)$, we have, for all $T > 0$, that:

$$\mathbb{P}\left[\left\{\sup_{0\leq t\leq T} \left|\left|f\left(X^N(t)\right) - \left(s(t), p(t)\right)\right|\right|_\infty > C_{N,\epsilon}e^{DT}\right\}\right] \leq 4\left[\exp\left(-\frac{\epsilon^2}{2A_fT}\right) + \exp\left(-\frac{\epsilon^2}{2A_gT}\right)\right],$$

Where

$$C_{N,\epsilon} = \epsilon + 3\frac{(k_1s_0 + k_2)}{k_2 + k_3}\left(\frac{m}{N} + \epsilon\right)$$

$$D = \frac{k_1k_3m}{k_2 + k_3}$$

$$A_f = \frac{em\left(k_1\left(s_0 + \frac{m}{N}\right) + (k_2 \vee k_3)\right)}{N}$$

$$A_g = \frac{em\left(k_1\left(s_0 + \frac{m}{N}\right) + (k_2 + k_3)\right)}{N}$$

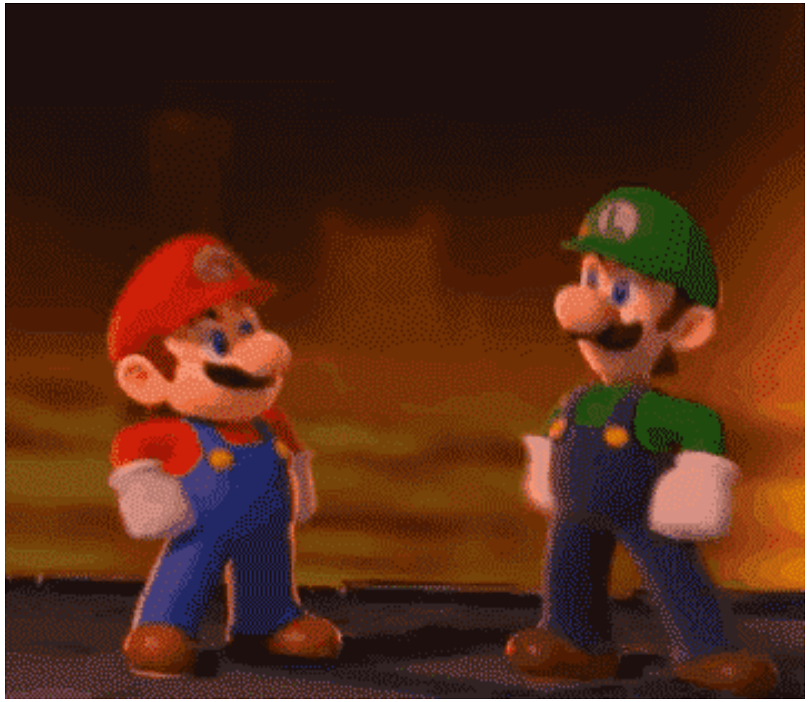
$$\frac{ds}{dt}(t) = -\frac{k_1ms(t)}{(k_2+k_3) + s(t)}$$

$$\frac{dp}{dt}(t) = \frac{k_1ms(t)}{(k_2+k_3) + s(t)}$$

Conclusion

Conclusion and Future Work

- Markov chains may converge to continuous dynamical systems under some appropriate scaling
- There are many different techniques to do so
- This is possible even when the system presents multiple time scales



Thank you for your attention!!