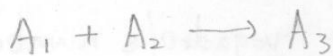


Biochemical Reaction Network (cont.)

V = volume $\times$ Avogadro's number

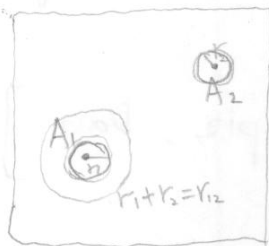
$\bar{x} = \frac{x}{V}$ where $x = \#$ molecules
↑
measure of concentration

Example:



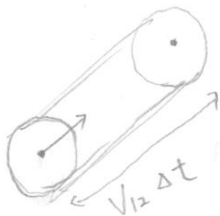
$$\lambda(x) = k x_1 x_2 = \frac{\tilde{k}}{V} x_1 x_2 = \tilde{k} V \bar{x}_1 \bar{x}_2$$

Idea for how $\lambda(x)$ depend on V



Consider a particular molecule of A_1 & molecule e of A_2

Assume spherical molecules of radius radius r_1 & r_2 respectively



V_{12} = speed of A_1 relative to A_2

In a small amount of time Δt , A_1 molecule sweeps out a volume $\approx \pi r_{12}^2 V_{12} \Delta t$

$r_{12} = r_1 + r_2$ is small compared to $\Delta t V_{12}$

Prob (Center of A_2 sphere is in volume swept out by A_1 in Δt)

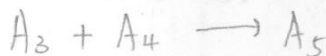
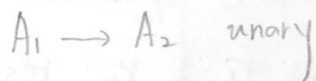
$$= \text{Prob} (A_1 \text{ reacts with } A_2 \text{ in } \Delta t)$$

$$\approx \frac{\pi r_{12}^2 V_{12} \Delta t}{(V/N)} \quad N = \text{Avogadro's number}$$

$$\text{Prob} (\text{some } A_1 \text{ reacts with some } A_2 \text{ in } \Delta t) \approx \lambda(x) \Delta t$$

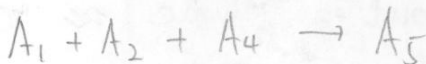
$$\approx (x_1 x_2) \frac{\pi r_{12}^2 V_{12} \Delta t}{(V/N)} \Rightarrow K \propto \frac{1}{V}$$

[Explanation due to Gillespie, Dan]



} binary reaction

can break into binary reaction



Approximate models for BCRN

$$X^r(t) = X^r(0) + \sum_{k=1}^K (v'_k - v_k) N_k \left(\int_0^t \lambda_k^r(X(s)) ds \right)$$

$$\lambda_k^r(x) = \frac{\tilde{K}_k \prod_{i=1}^n v_{ik} \cdot \frac{x_i}{v_{ik}}}{V^{m_k-1}} \quad m_k = \sum_{i=1}^n v_{ik}$$

(Consider a sequence of systems indexed by $r = V$)

Define $\bar{X}^r(t) = \frac{X^r(t)}{r}$ = concentration in r^{th} system at time t

$$\bar{X}^r(t) = \bar{X}^r(0) + \sum_{k=1}^K (v'_k - v_k) \frac{1}{r} N_k \left(r \int_0^t \underbrace{\frac{1}{r} \lambda_k^r(X^r(s))}_{f_k^r(\bar{X}^r(s))} ds \right)$$

where

$$f_k^r(\bar{X}^r) = \frac{1}{r} \tilde{K}_k \frac{\prod_{i=1}^n (X_i (X_i - 1) \dots (X_i - v_{ik} + 1))}{V^{m_k-1}}$$

$$= \tilde{K}_k \prod_{i=1}^n \bar{X}_i^r (\bar{X}_i^r - \frac{1}{r}) \dots (\bar{X}_i^r - \frac{v_{ik}-1}{r})$$

Assume $\bar{X}^r(0) \Rightarrow \bar{X}(0)$ as $r \rightarrow \infty$

Strong Approximation Theorem (Komlos, Major, Tusnady. 1975)

There is a probability space on which there is a unit rate Poisson process N and a standard 1-diml Brownian motion W such that

$$\sup_{t \geq 0} \frac{|N(t) - t - W(t)|}{(\log t) \vee 2} = \eta < \infty \text{ a.s.}$$

$\uparrow$
max.

where $E[e^{\alpha \eta}] < \infty$ for some $\alpha > 0$

$$N(t) = t + W(t) + \ell(t) \xi(t), \quad \ell(t) = \log t \vee 2$$

$$\text{where } |\xi(t)| \leq \eta \quad \forall t$$

$\Rightarrow$

There is a prob. space with indep. Poisson process

$N_1, \dots, N_k$ and indept. Brownian motion $W_1, \dots, W_k$

$$\text{s.t.} \quad \sup_{t \geq 0} \frac{|N_k(t) - t - W_k(t)|}{\ell(t)} = \eta_k$$

where $E[e^{\alpha \eta_k}] < \infty$

for some $\alpha > 0$

$\Rightarrow$

$$\begin{aligned} \bar{X}^r(t) = \bar{X}^r(0) + & \sum_{k=1}^K (v_k' - v_k) \left[\int_0^t f_k^r(\bar{X}^r(s)) ds + \frac{1}{r} w_k(r \int_0^t f_k^r(\bar{X}^r(s)) ds) \right. \\ & \left. + \frac{1}{r} l(r \int_0^t f_k^r(\bar{X}^r(s)) ds) \cdot \sum_{k=1}^K (r \int_0^t f_k^r(\bar{X}^r(s)) ds) \right] \end{aligned}$$

Idea: i) Prove $\{\bar{X}^r\}_{r>0}$ is C-tight

ii) Establish eqn that any limit pt. satisfies

C-tight criterion

$\{\bar{X}^r\}$ is C-tight if for each $T > 0$ & $\varepsilon > 0$

there are $\delta^* = \delta(\varepsilon, T)$, $K^* = K(\varepsilon, T)$ & $r^* = r(\varepsilon, T)$

s.t. $\forall r \geq r^*$

compact containment $\Rightarrow$

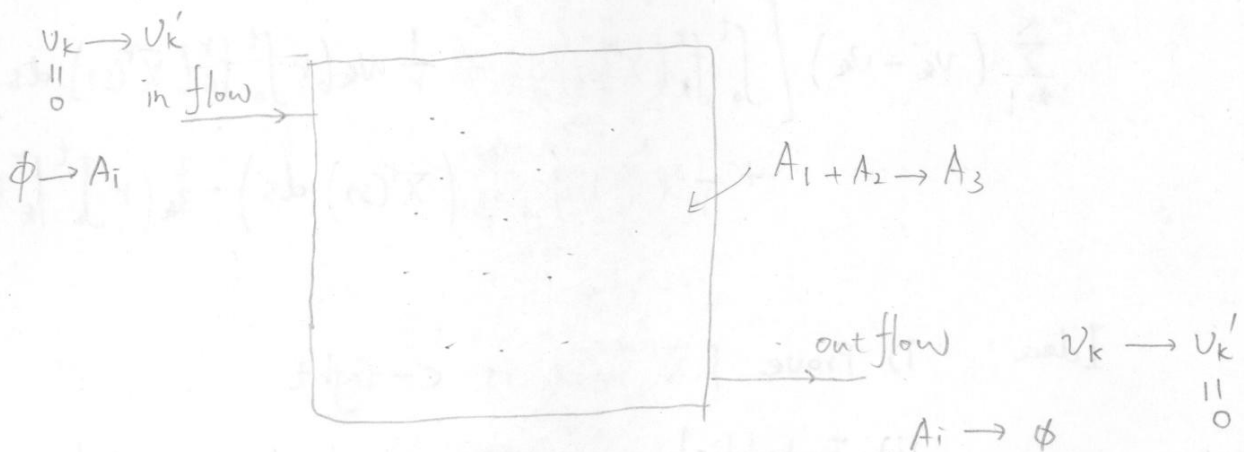
$$i) P(\|\bar{X}^r\|_T \geq K^*) < \varepsilon \quad \|X\|_T = \sup_{t \in [0, T]} |X(t)|$$

$$ii) P(\underbrace{w(\bar{X}^r, \delta^*, T)}_{\substack{\sup_{t \in [0, T-\delta]} \sup_{u, v \in [t, t+\delta]} |\bar{X}^r(u) - \bar{X}^r(v)|}} \geq \varepsilon) < \varepsilon$$

$$\sup_{t \in [0, T-\delta]} \sup_{u, v \in [t, t+\delta]} |\bar{X}^r(u) - \bar{X}^r(v)|$$

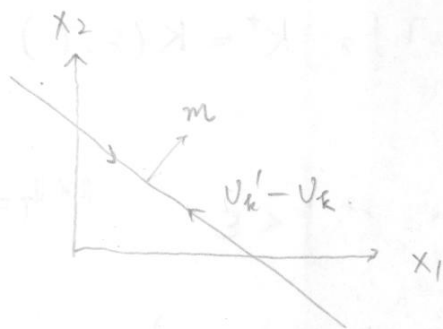
measures oscillations

Assume continuous flow stirred tank reactor



Conserved quantity

A vector $m \in \mathbb{R}_+^n$, $m > 0$, is a conserved quantity for all reactions if $m \cdot (v'_k - v_k) = 0 \quad \forall k$



Assume that $m > 0$ is a conserved quantity for reactions

$$k=1, \dots, K_1$$

Assume reactions $k=K_1+1, \dots, K_2$ are outflow reactions

and $k=K_2+1, \dots, K$ are inflow reactions

$$\begin{aligned} \text{Then } m \cdot \bar{X}^r(t) &\leq m \bar{X}^r(0) + \sum_{k=K_2+1}^K \underbrace{m \cdot (V'_k - V_k)}_{d_k > 0} \\ &\quad \cdot \left[\tilde{K}_k t + \underbrace{\frac{1}{r} W_k(r \tilde{K}_k t)}_{\parallel d} + \frac{1}{r} l(r \tilde{K}_k t) \underbrace{\xi_k(r \tilde{K}_k t)}_{\leq \eta_k} \right] \\ &\quad \frac{\mathbb{P}}{r} \tilde{W}_k(\tilde{K}_k t) \Rightarrow 0 \text{ as } r \rightarrow \infty \end{aligned}$$

$$\frac{1}{r} l(r \tilde{K}_k t) = \frac{(\log(r \tilde{K}_k t)) \vee 2}{r} \rightarrow 0 \text{ as } r \rightarrow \infty$$

$$m \cdot \bar{X}^r(0) \Rightarrow m \cdot \bar{X}(0)$$

It follows that given $T, \varepsilon > 0 \exists k^*, r^*$ s.t.

$$\mathbb{P}(\|m \cdot \bar{X}^r\|_T \geq k^*) < \varepsilon \quad \forall r \geq r^*$$

Since $m > 0 \exists \tilde{K}^*$ s.t.

$$\mathbb{P}(\|\bar{X}^r\|_T \geq \tilde{K}^*) < \varepsilon \quad \forall r \geq r^*$$

Gives compact containment

$$f_k^r(x) = \tilde{K}_k \prod_{i=1}^n \left(\bar{x}_i \left(\bar{x}_i - \frac{1}{r} \right) \cdots \left(\bar{x}_i - \left(\frac{V_{ik}-1}{r} \right) \right) \right)$$

Define

$$f_k(x) = \tilde{K}_k \prod_{i=1}^n x_i^{V_{ik}} \quad x \in \mathbb{R}_+^n$$

$$= \tilde{K}_k x^{V_k}$$

$f_k^r \rightarrow f_k$ uniformly on compact sets in $\mathbb{R}_+^n$
as $r \rightarrow \infty$

Fix $\varepsilon > 0$, $T > 0$

Let $G^{\varepsilon, r} = \{ \|\bar{X}^r\|_T < K^* \} = \text{"good" set}$

Know: $P(G^{\varepsilon, r}) \geq 1 - \varepsilon$

On $G^{\varepsilon, r}$, $\exists m^* = m(\varepsilon, T)$ s.t.

$$\|f_k(\bar{X}^r(\cdot))\|_T \leq m^* \text{ and } \|f_k^r(\bar{X}^r(\cdot))\|_T \leq m^*$$

for $r \geq r^*$

$$\bar{X}^r(t) = \bar{X}^r(0) + \sum_{k=1}^K (V_k' - V_k) \frac{1}{r} N_k(r) \int_0^t f_k^r(\bar{X}^r(s)) ds$$

$$= \bar{X}^r(0) + \sum_{k=1}^K (V_k' - V_k) \bar{N}_k^r \left(\int_0^t f_k^r(\bar{X}^r(s)) ds \right)$$

$$\text{where } \bar{N}_k^r(\cdot) = \frac{N_k(r, \cdot)}{r}$$

$$(\bar{N}_1^r(\cdot), \dots, \bar{N}_K^r(\cdot)) \Rightarrow (1(\cdot))$$

$$1(t) = (1, \dots, 1)t$$

$$\text{let } \Phi_k^r(t) = \int_0^t f_k^r(\bar{X}(s)) ds$$

Claim: $\{\Phi_k^r; k=1, \dots, K\}$ is C -tight

$$(i) \quad P(\|\Phi_k^r\|_T \geq M^* T) \leq P((G^{\varepsilon, r})^c) < \varepsilon$$

$$(ii) \quad P(w(\Phi_k^r, \delta, T) > M^* \delta) \leq P((G^{\varepsilon, r})^c) < \varepsilon$$

we have

$$\{(\bar{N}_1^r, \dots, \bar{N}_K^r, \Phi_1^r, \dots, \Phi_K^r, \bar{X}^r)\}_{r>0} \text{ is } C\text{-tight}$$

Any weak limit point

$$(1(\cdot), \Phi_1, \dots, \Phi_K, \bar{X})$$

satisfies

$$\bar{X}(t) = \bar{X}(0) + \sum_{k=1}^K (V_k' - V_k) \int_0^t f_k(\bar{X}(s)) ds$$

$\bar{X}(t)$ = conc. at time t

$$\dot{\bar{X}}(t) = S r(\bar{X}(t))$$

$$\text{where } r_k(\bar{X}(t)) = f_k(\bar{X}(t))$$

e.g. $v_k \rightarrow v_k'$



$$f_k(\bar{x}) = K_k \bar{x}_1 \bar{x}_2$$

$$\bar{x}^r \Rightarrow \bar{x} \text{ since } \bar{x} \text{ is unique given } \bar{x}(0).$$