(J. Maas) . 21/01/2015.

Chemical reaction networks.

$$\alpha_1^r X_1 + \cdots + \alpha_d^r X_d \underset{k_{bw}}{\overset{k_{fw}}{\rightleftharpoons}} \beta_1^r X_1 + \cdots + \beta_d^r X_d .$$

$\in \mathbb{N}$, r - reactions (directions). $r = 1, \ldots, R$. reaction can happen forward and backwards.

k_{fw} - forward reaction rate
k_{bw} - backward reaction rate.

Two models: (I) stochastic, discrete
(II) deterministic, continuous.

(I) Stochastic model.

- observable $\underline{N} = (N_1, \ldots, N_d) \in \{0, 1, \ldots, \}^d$.
  (N_i := number of particles of species X_i)
- $N(t)$ evolves according to a ct. time markov chain (CTMC). with rates:

  (*) from $\underline{n}$ to $\underline{n} - \underline{\alpha}^r + \underline{\beta}^r$: $k_{fw}^r \cdot \prod_{i=1}^d \frac{n_i!}{(n_i - \alpha_i^r)!} \cdot \frac{1}{\mathrm{vol}^{|\alpha| - 1}}$.

  (*) from $\underline{n}$ to $n + \underline{\alpha}^r - \underline{\beta}^r$: $k_{bw}^r \cdot \prod_{i=1}^d \frac{n!}{(n - \beta_i^r)!} \frac{1}{\mathrm{vol}^{|\beta| - 1}}$.

Let $u(t) \in \mathcal{P}(\mathbb{N}_0^d)$ be the law of $N(t)$. Then $n(t)$ satisfies the chemical master equation.

(II) deterministic model:

- observable $\underline{c} = (c_1, \ldots, c_d) \in \mathbb{R}_+^d$; concentration of the species X_i.
- $\underline{c}(t)$ evolves according to reaction rate eqn.:

$$\dot{\underline{c}} = -\underline{R}(\underline{c}) , \quad \dot{c}_i(t) = -\sum_{r=1}^R \left(k_{fw}^r \cdot \prod_{j=1}^d c_j(t)^{\alpha_j^r} - k_{bw}^r \prod_{j=1}^d c_j(t)^{\beta_j^r} \right).$$

• Let $\rho(t)$ be a prob measure $\in \mathcal{P}(\mathbb{R}^d_+)$ be the law of $\underline{c}(t) \in \mathbb{R}^d_+$. Then, $\rho(t)$ evolves according to the Liouville eq:

$$\partial_t \rho(c) = \mathrm{div}\,(\rho(c)\, R(c)).$$

$$\begin{array}{ccc}
n(t) \in \mathcal{P}(\mathbb{N}_0^d) & & \rho(t) \in \mathcal{P}(\mathbb{R}^d_+) \\
\text{CME} & & \text{Liouville} \\
\uparrow & & \uparrow \\
N(t) \in \mathbb{N}_0^d & \longrightarrow & c(t) \in \mathbb{R}^d_+ \\
\text{CTMC} & & \text{RRE}
\end{array}$$

Kurtz 1970's
rescaled Markov C. converges to $c(t)$:
(i.e., if $N(0)/\mathrm{vol} \to c_0$,
$N(t)/\mathrm{vol} \longrightarrow c(t)$)

• Gradient flows. ~~Assume~~.

Assume. $\exists\ \underline{c}^* := (c_1^*, \dots, c_d^*) \in \mathbb{R}^d_{>0}$ s.t.

$$k_*^r := k_{fw}^r \cdot \prod_{j=1}^d (c_j^*)^{\alpha_j^r} = k_{bw}^r \cdot \prod_{j=1}^d (c_j^*)^{\beta_j^r} \quad \forall r = 1, \dots, R.$$

Then CME, RRE, two have gradient flow structures

• CME: $\dot{n} = -\mathcal{K}(n) D\mathcal{E}(n)$. : $\mathcal{E}(n) = \mathrm{Ent}(n \mid w^V)$.

$$(w^V)_{\underline{n}} = e^{-V|\underline{c}^*|} \cdot \frac{\underline{c}_*^{\underline{n}} V^{|n|}}{n!}$$

($\mathcal{K}$ - pos. def. infinite dim matrix
~ inverse of Riem. metric.)

• RRE (Mielke): $\dot{c} = K(c) DE(c)$. $\quad E(c) = \mathrm{Ent}(\underline{c} \mid \underline{c}^*)$.

$$K(c) := \sum_r k_*^r\, \theta\!\left(\frac{c^{\alpha^r}}{c_*^{\alpha^r}}, \frac{c^{\beta^r}}{c_*^{\beta^r}}\right) (\underline{\alpha}^r - \underline{\beta}^r) \otimes (\underline{\alpha}^r - \underline{\beta}^r).$$

$E(\underline{c}) = \sum_{i=1}^d c_i^* h\left(\frac{c_i}{c_i^*}\right)$, $h(t) = t \log(t) - t + 1$.

- Liouville: $\dot{\rho} = -\mathbb{K}(\rho) D\mathbb{E}(\rho)$, $\mathbb{E}(\rho) = \int E(c)\, d\rho(c)$.

$$(\mathbb{K}(\rho)\varphi)(c) = -\operatorname{div}(\rho(c) K(c) \nabla \varphi(c)).$$

Induced distance is W_2 with underlying Riem metric K^{-1}.

Set $\Psi^*_{\mathrm{CME}}(\mu, \xi) = \frac{1}{2}\langle \xi, \mathcal{K}(\mu)\xi\rangle$, $\mu \in \mathcal{P}(\mathbb{N}_0^d)$, $\xi : \mathbb{N}_0^d \to \mathbb{R}$.

$$\Psi^*_{\mathrm{Lio}}(\rho, \varphi) = \frac{1}{2}\langle \varphi, \mathbb{K}(\rho)\varphi\rangle = \frac{1}{2}\int \langle \nabla\varphi(c), K(c)\nabla\varphi(c)\rangle\, d\rho(c). \quad \Bigg| \begin{array}{l}\rho \in \mathcal{P}(\mathbb{R}_+^d) \\ \varphi : \mathbb{R}_+^d \to \mathbb{R}\end{array}$$

<u>Prop</u> (M-Mielke) $\quad \Psi^*_{\mathrm{CME}} \xrightarrow[V\to\infty]{} \Psi^*_{\mathrm{Lio}}$.

<u>Passing to the limit</u> "$\frac{1}{V}\mathcal{E} \to \mathbb{E}$".

Recall: $\frac{1}{V}\mathcal{E}(\mu) = \underbrace{\frac{1}{V}\sum_{n\in\mathbb{N}_0^d} u_n \log u_n}_{\mathcal{E}_V^1(\mu)} - \underbrace{\frac{1}{V}\sum_n u_n \log w_n}_{\mathcal{E}_V^2(\mu)}$.

Study limit $V\to\infty$, $n_k \to \infty$, $n_k/V \to c_k$.

Sps $\mu \in \mathcal{P}(\mathbb{N}_0^d)$ which approximates $\rho \in \mathcal{P}(\mathbb{R}_+^d)$.

$$\mathcal{E}_V^1(\mu) \approx \frac{1}{V}\int \rho(c)\log\rho(c) - d\,\frac{\log V}{V} \xrightarrow[\text{as } V\to\infty]{} 0$$

Now, $\quad -\frac{1}{V}\log w_n^V = \sum_{i=1}^d \left[-\frac{n_i}{V}\log(Vc_i^*) + \frac{\log n_i!}{V} + c_i^*\right]$

$$\overset{*}{\approx} E\left(\frac{n}{V}\right).$$

(Stirling $\log n! \approx n\log n - n$.)

Thus: $\frac{1}{V}\mathcal{E}(n) \approx \sum E(\tfrac{n}{V}) x_n \simeq \int E(c)\, d\rho(c) = \mathbb{E}(\rho)$.

$\rightsquigarrow$ Liouville eq^n is a good approx to CME for large V.

N.B. Liouville does not take volume into account. Can we find a better one which takes this into account. The gradient flow approach is suggestive in this direction.

First guess: set $\tilde{\mathbb{E}}_V(\rho) = \int E(c)\, d\rho(c) + \frac{1}{V}\int \rho(c) \log \rho(c)\, dc$.

$\rightsquigarrow$ Associated gradient flow eq^n.

$$\partial_t \rho = - \mathbb{K}(\rho) D\tilde{E}_V(\rho).$$

(Fokker-Planck eq.).

(This only considers first term we threw away).

~~A that~~

A better approx: $\rightarrow$ Take into account terms we threw away from using Sterling's formula in 2nd term.

$$\log n! \simeq n \log n - n + \frac{1}{2}\log\left[2\pi\left(n+\frac{1}{6}\right)\right].$$

$$\rightsquigarrow \quad -\frac{1}{V}\log W_n^V \approx E\left(\tfrac{n}{V}\right) + \frac{1}{V} G_V\left(\tfrac{n}{V}\right).$$

$$G_V(c) = \frac{1}{2}\sum_i \log\left(2\pi\left(Vc_i + \frac{1}{6}\right)\right).$$

$\Rightarrow$ This leads to : $\mathbb{E}_V(\rho) = \mathbb{E}(\rho) + \frac{1}{V}\int \rho \log \rho + \frac{1}{V}\int G_V(c)\, d\rho(c)$

New equation : $\dot{\rho} = -\mathbb{K}(\rho) D\, \mathbb{E}_V(\rho)$.

$$\partial_t \rho = -\,\mathrm{div}\Big[\rho(c)\, R(c) + \tfrac{1}{V}\mathbb{K}(c)\, \nabla \rho(c) + \rho(c)\, A_V(c)\Big].$$

where $A_V(c) = \frac{1}{2}\,.\,\mathbf{k}(c)\Big(\frac{1}{Vc_i + \frac{1}{6}}\Big)_{i=1,\dots d}$.