Global asymptotic stability of solutions of nonautonomous master equations

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satisfy the *Chapman-Kolmogorov equations*

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$$a_{ij} \text{ right-continuous}, \quad a_{ij} \geq 0 \ (i \neq j), \quad a_{jj} = -\Sigma_{i \neq j} a_{ij}$$

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$$\frac{d\mathbf{p}_i}{dt} = A(t)\mathbf{p}_i$$

$$A(t) = (a_{ij}(t)), \quad \mathbf{p}_i = (p_{i0}, \ldots, p_{in})^T, \quad p_{ij}(t) = p(i,t|j,0)$$

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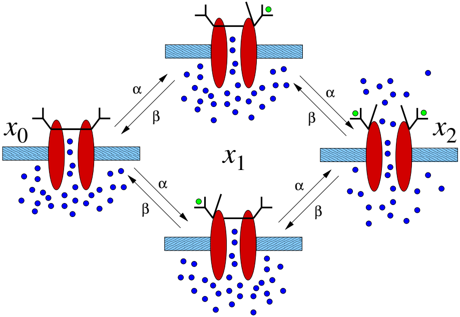
- Matrices like $A(t)$ called $\mathbb{W}$-matrices [van Kampen]

Ion channel with two identical, independent subunits



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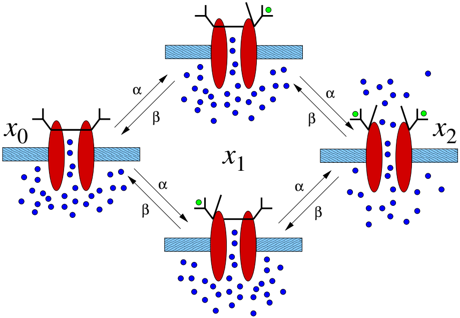

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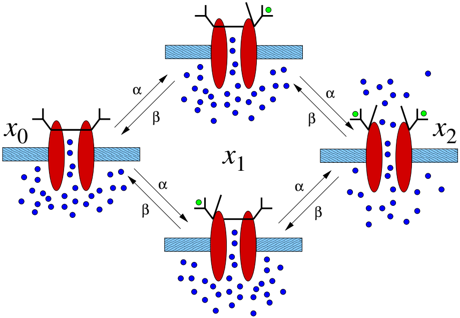

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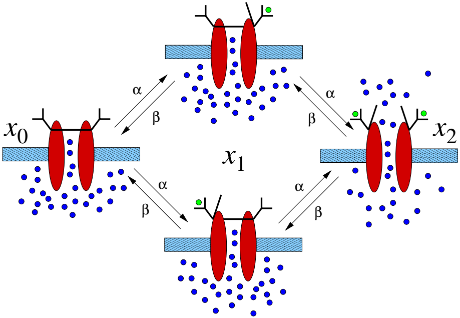

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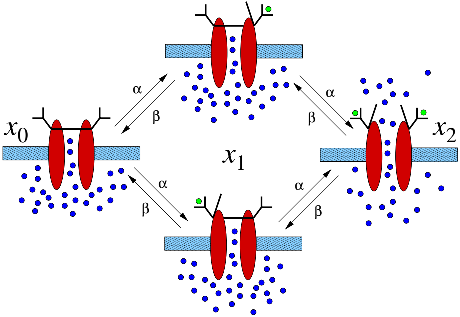

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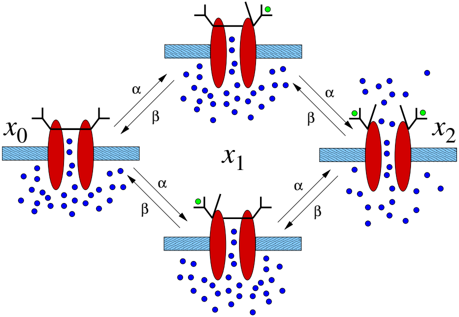
State diagram: $x_0 \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} x_1 \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} x_2$

Master equation for ion channel kinetics



$$x_0 \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} x_1 \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} x_2$$

- $\mathbf{p}(t) = (p_0(t), p_1(t), p_2(t))^T$ = probability distribution for $X(t)$

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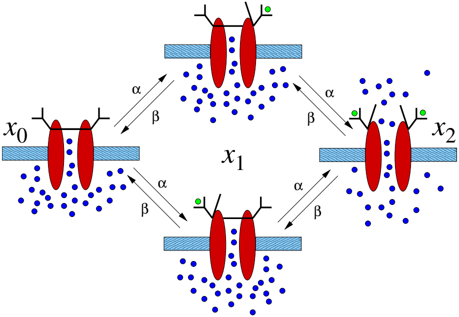

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Master equation: $$\frac{d\mathbf{p}}{dt} = A\mathbf{p} = \begin{bmatrix} -2\alpha & \beta & 0 \\ 2\alpha & -\alpha-\beta & 2\beta \\ 0 & \alpha & -2\beta \end{bmatrix} \begin{bmatrix} p_0 \\ p_1 \\ p_2 \end{bmatrix}$$

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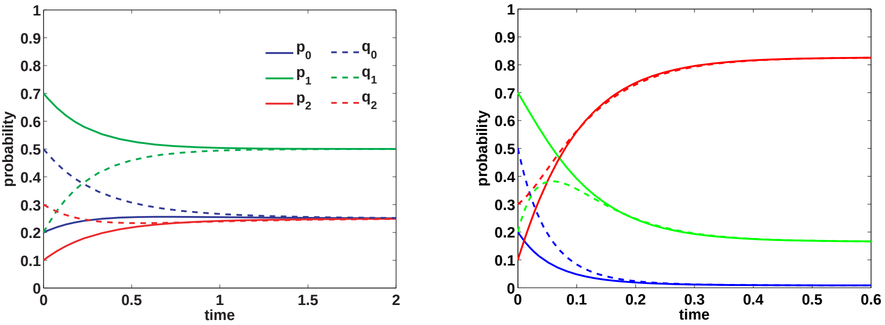
$\alpha = \beta = 1$ $\alpha = 10,\ \beta = 1$



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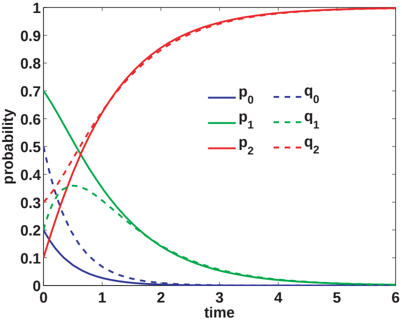

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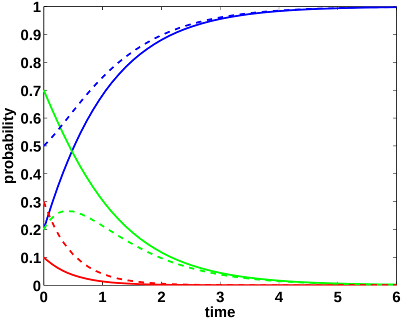

van Kampen's theorem for autonomous master equations

Theorem

Suppose A is a constant $\mathbb{W}$-matrix. If A is neither decomposable nor splitting, then every probability distribution solution of the master equation approaches a unique stationary distribution.

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A is *decomposable* if there exists permutation matrix P such that

$$P^{-1}AP = \begin{bmatrix} A_1 & 0 \\ 0 & A_2 \end{bmatrix}$$

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where $\mathbf{v}_i$'s are eigenvectors and c_i's are polynomials in t

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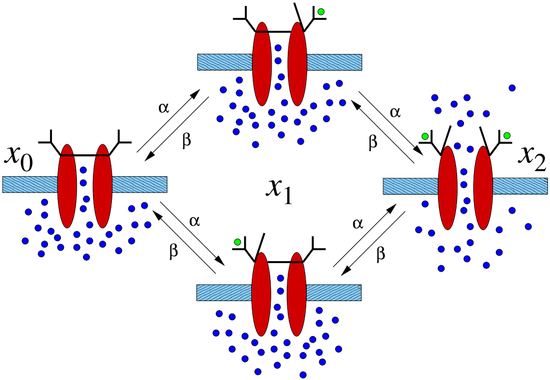
where $\mathbf{v}_i$'s are eigenvectors and c_i's are polynomials in t
- Therefore, $\mathbf{p}(t) \to \mathbf{v}_0$ independent of initial conditions
- Note: converse of theorem is also true

Nonautonomous master equation



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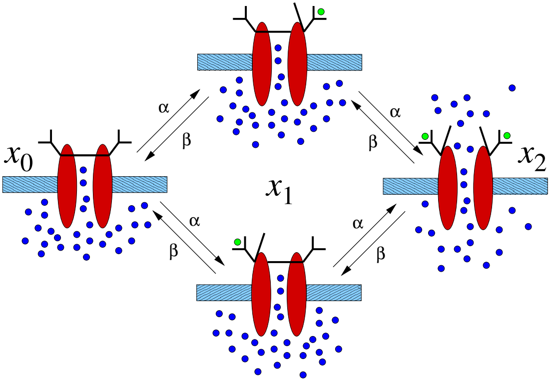

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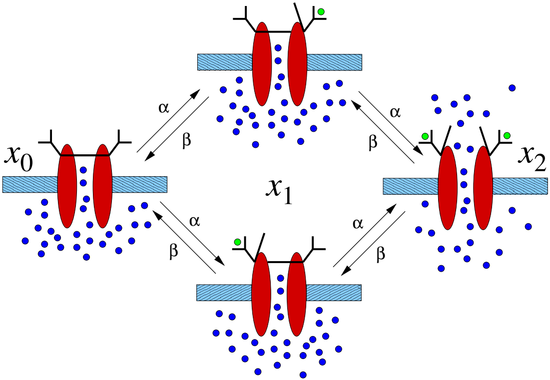

- Ion channel kinetics are dependent on *external* factors – e.g., membrane voltage and ligand concentration
- Open and close rates α, β are functions of time!
- How will solutions behave now?

Behavior of solutions of nonautonomous master equation

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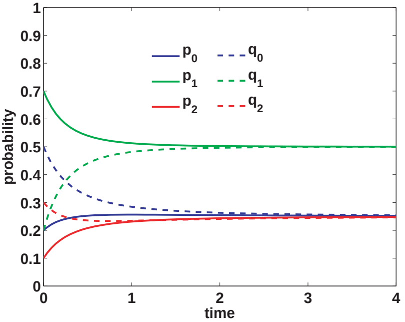
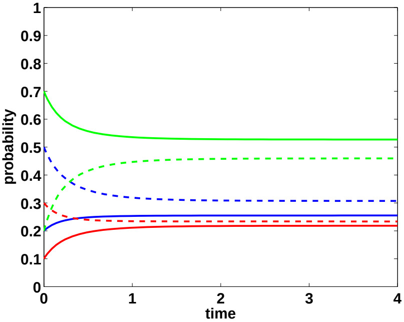
$\alpha = \beta = (t+1)^{-1}$



$\alpha = \beta = \exp(-2t)$



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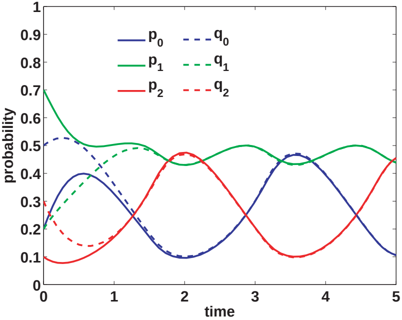
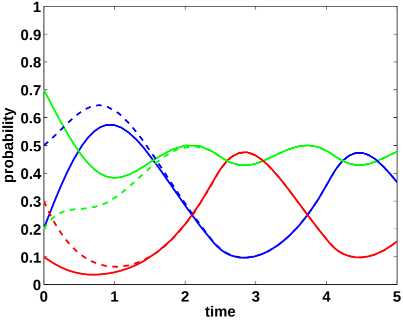
$\alpha = |\sin(t)|,\ \beta = |\cos(t)|$



$\alpha = \left|\sin(te^{-1/t})\right|,\ \beta = \left|\cos(te^{-1/t})\right|$



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$\alpha = \Theta(\sin(\pi t)),\ \beta = \Theta(\cos(\pi t))$

$\alpha = \sin(2\tan^{-1}(100t)),$
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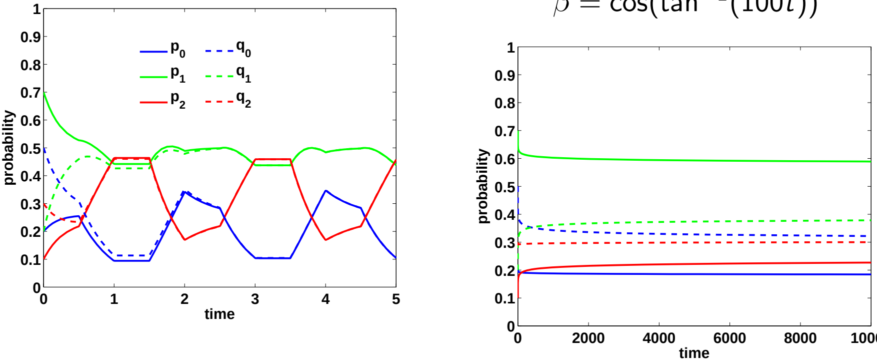

What causes solutions to approach each other?

Current theory

If the transition rates vary according to specific functions of time, the concentration of each subunit state approaches to a specific function of time (in comparison to a constant value when transition rates are constant) regardless of the initial concentration of states.

Nekouzadeh, Silva and Rudy, *Biophys J* (2008)

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$$
\begin{aligned}
a_{11}(t) &= -1 - 9\cos^2(6t) + 12\sin(6t)\cos(6t) \\
a_{12}(t) &= 12\cos^2(6t) + 9\sin(6t)\cos(6t) \\
a_{21}(t) &= -12\sin^2(6t) + 9\sin(6t)\cos(6t) \\
a_{22}(t) &= -1 - 9\sin^2(6t) - 12\sin(6t)\cos(6t)
\end{aligned}
$$

$A(t) = (a_{ij}(t))$ has eigenvalues -1 and -10 for all $t \geq 0$, yet

$$
\mathbf{x}(t) = e^{2t}\begin{bmatrix} 2\sin(6t) + \cos(6t) \\ 2\cos(6t) - \sin(6t) \end{bmatrix} + 2e^{-13t}\begin{bmatrix} 2\cos(6t) - \sin(6t) \\ 2\sin(6t) - \cos(6t) \end{bmatrix}
$$

is a solution of $\dot{\mathbf{x}} = A(t)\mathbf{x}$

$\mathcal{L}^1$-norm as Lyapunov function for H_0-solutions

- Recall $||\mathbf{x}||_1 = \sum_{i=1}^{n} |x_i|$

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- If $\mathbf{x}(t)$ is any H_0-solution, then for a.e. t:

$$\frac{d||\mathbf{x}(t)||_1}{dt} = -\sum_{i\in[n]\setminus I_+}\sum_{j\in I_+} a_{ij}(t)x_j(t) - \sum_{i\in[n]\setminus I_-}\sum_{j\in I_-} a_{ij}(t)\,|x_j(t)|$$
$$-\sum_{i\in I_-}\sum_{j\in I_+} a_{ij}(t)x_j(t) - \sum_{i\in I_+}\sum_{j\in I_-} a_{ij}(t)\,|x_j(t)|$$

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$\mathcal{L}^1$-norm as Lyapunov function for H_0-solutions

- Recall $||\mathbf{x}||_1 = \sum_{i=1}^n |x_i|$
- Define $H_0 = \{\mathbf{x} \mid \sum_{i=1}^n x_i = 0\}$
  - H_0 is invariant manifold of master equation
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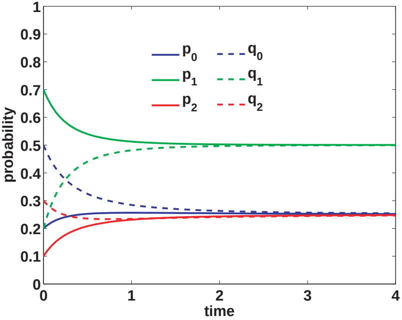
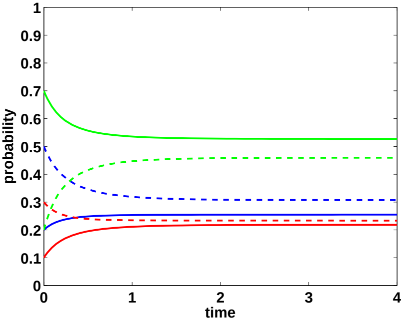
- If $\frac{d||\mathbf{x}(t)||_1}{dt} = 0$ then $A(t)$ is decomposable or splitting ($\Rightarrow \lambda_1(t) = 0$)
- Contrapositive: if $\Re(\lambda_1(t)) < 0$ then $\frac{d||\mathbf{x}(t)||_1}{dt} < 0$

First extension of van Kampen's theorem

$$\alpha(t) = \beta(t) = (t+1)^{-1}$$



$$\alpha(t) = \beta(t) = \exp(-2t)$$



$$A(t) = \alpha(t)\begin{bmatrix} -2 & 1 & 0 \\ 2 & -2 & 2 \\ 0 & 1 & -2 \end{bmatrix}$$

First extension of van Kampen's theorem

Theorem

Suppose $A(t) = f(t)M$ *for all* $t \geq 0$, *where* M *is constant* $\mathbb{W}$*-matrix and* $f : \mathbb{R}_+ \to \mathbb{R}_+$ *is continuous. Then every probability distribution solutions of the master equation approaches a unique stationary distribution if and only if* M *is neither decomposable nor splitting and* f *is not integrable.*

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- Proof similar to van Kampen's theorem since FMS is

$$\Phi_0^t = \exp\left(\int_0^t A(t)\right) = \exp\left(F(t)M\right) \quad \left(F(t) = \int_0^t f(s)\,ds\right)$$

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- Hence every probability distribution solution $\mathbf{p}$ is of form

$$\mathbf{p}(t) = \mathbf{v}_0 + c_1 e^{\mu_1 F(t)}\mathbf{v}_1 + \cdots + c_n e^{\mu_n F(t)}\mathbf{v}_n$$

where $\mu_i, \mathbf{v}_i$ are eigenpairs of M and c_i's are polynomials in $F(t)$

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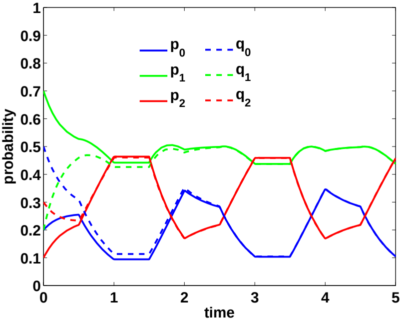
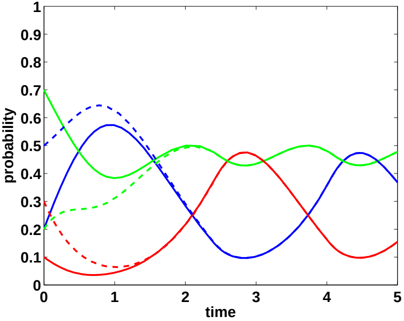
- $\mathbf{p}(t) \to \mathbf{v}_0 \Leftrightarrow \Re(\mu_i) < 0$ for $i = 1, \ldots, n$, and $F(t) \to \infty$

Extension for asymptotically periodic A

$\alpha = \Theta(\sin(\pi t))$, $\beta = \Theta(\cos(\pi t))$



$\alpha = \left|\sin(te^{-1/t})\right|$, $\beta = \left|\cos(te^{-1/t})\right|$



- In both cases, A approaches a periodic matrix

Extension for asymptotically periodic A

Definition

The probability distribution solutions of a master equation are *globally asymptotically stable* (GAS) if for every pair of such solutions $\mathbf{p}, \mathbf{q}$

$$\mathbf{p}(t) - \mathbf{q}(t) \to \mathbf{0} \text{ as } t \to \infty.$$

Theorem

Suppose A is a continuous, $\mathbb{W}$-matrix-valued function, and that there exists a continuous, periodic, $\mathbb{W}$-matrix-valued function B, whose ω-limit set contains at least one matrix that is neither decomposable nor splitting, such that

$$\lim_{t\to\infty} ||A(t) - B(t)|| = 0.$$

Then the probability distribution solutions of the master equation are GAS.

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- Proof: $\mathcal{L}^1$-norm of H_0-solutions of $\dot{\mathbf{x}} = B\mathbf{x}$ must decrease by some uniform, nonzero amount during each period of B.

Another extension of van Kampen's theorem

Theorem

If A is differentiable, $\mathbb{W}$-matrix-valued function such that both A and its derivative are bounded, and the ω-limit set of A contains no matrix which is either decomposable or splitting, then probability distribution solutions of the master equation are GAS.

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If A is differentiable, $\mathbb{W}$-matrix-valued function such that both A and its derivative are bounded, and the ω-limit set of A contains no matrix which is either decomposable or splitting, then probability distribution solutions of the master equation are GAS.

- Proof: if $||\mathbf{x}(t)||_1 \to r > 0$, then $\omega(A)$ contains a decomposable or splitting matrix

One might conjecture...

- Let $\lambda_0, \lambda_1, \dots, \lambda_n$ be an ordering of the eigenvalues of A such that

$$0 = \lambda_0(t) \geq \Re(\lambda_1(t)) \geq \cdots \geq \Re(\lambda_n(t))$$

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- The nonintegrability of $\Re(\lambda_1)$ "should" ensure that $||\mathbf{x}(t)||_1 \to 0$

Counterexample for conjecture

$$A(t) = \frac{1-\cos(\pi t)}{2} A_1(t) + \frac{1-\cos(\pi(t+1))}{2} A_2(t)$$

$$A_1(t) = \begin{bmatrix} -1 & 0 & 0 & 0 \\ 1 & -\frac{1}{t+1} & 0 & 0 \\ 0 & \frac{1}{t+1} & -\frac{1}{t+1} & 0 \\ 0 & 0 & \frac{1}{t+1} & 0 \end{bmatrix}, \quad A_2(t) = \begin{bmatrix} -\frac{1}{t+1} & \frac{1}{t+1} & 0 & 0 \\ 0 & -\frac{1}{t+1} & 1 & 0 \\ 0 & 0 & -1 & 0 \\ \frac{1}{t+1} & 0 & 0 & 0 \end{bmatrix},$$

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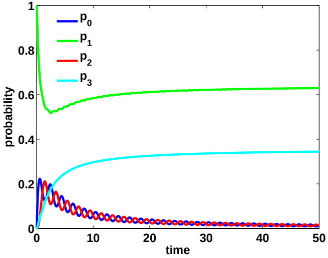

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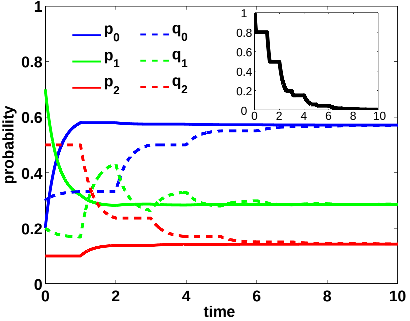

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Conjecture

If the derivative of A is bounded and the ω-limit set of contains at least one matrix which is neither decomposable nor splitting, then the probability distribution solutions of the master equation are GAS.

Thank you!

Thanks to

- Jim Keener (Utah)
- NSF