Global asymptotic stability of solutions of nonautonomous master equations

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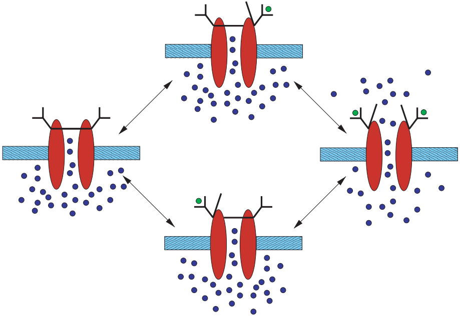
Ion channel with two identical subunits



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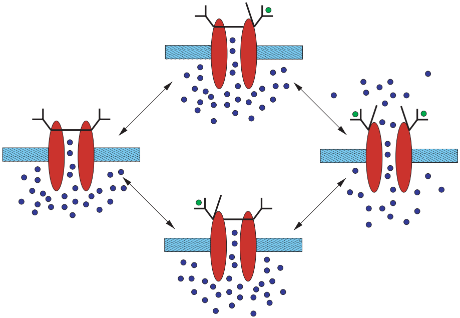

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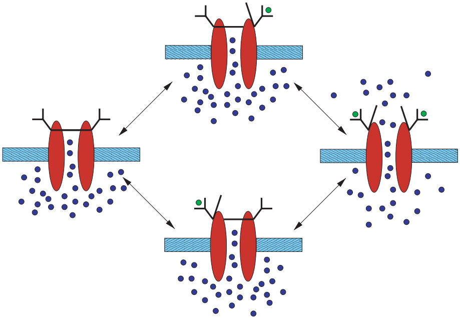

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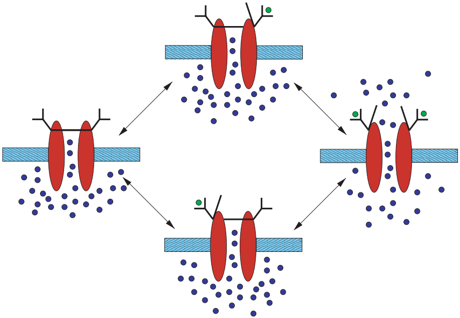

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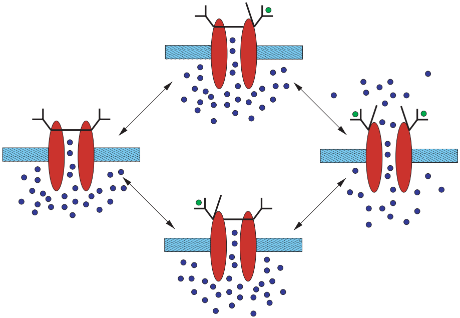

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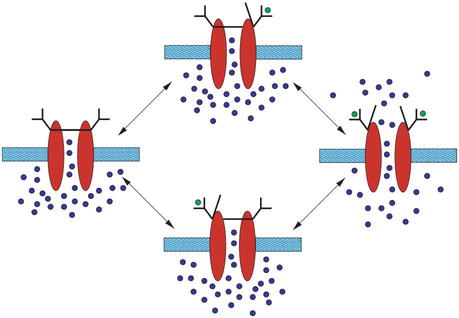
    - channel has 3 states: S_0, S_1, S_2 ($i = \#$ open subunits)
- Subunits open, close randomly at rates α, β
- If $X(t) \in \{S_0, S_1, S_2\}$ denotes channel state at time $t \geq 0$, then X is a *jump process*

$$S_0 \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} S_1 \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} S_2$$

Master equation for jump process



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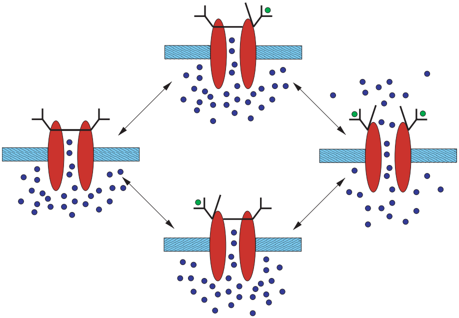

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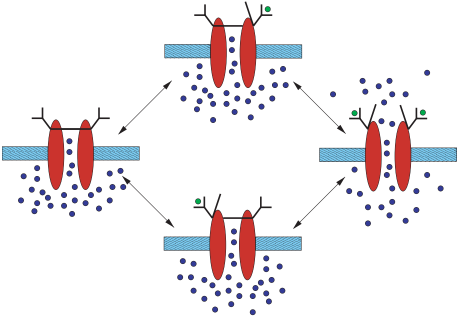

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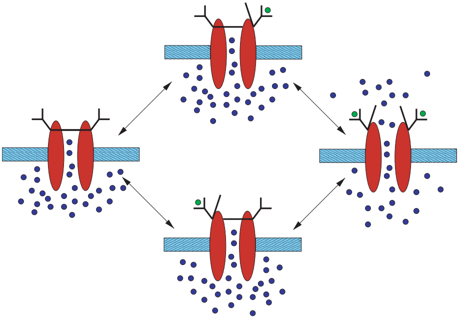

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- From state diagram we derive *master equation* for $\mathbf{p}$

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

Invariant manifolds of master equation

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2. off-diagonal entries nonnegative $\Rightarrow K = \{\mathbf{p} \in \mathbb{R}^3 \mid \mathbf{p} \geq \mathbf{0}\}$ is invariant

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   - Probability distributions remain probability distributions!

Behavior of solutions of autonomous master equation

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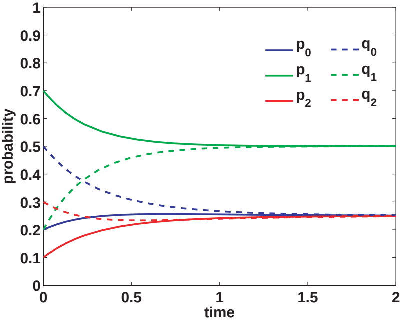
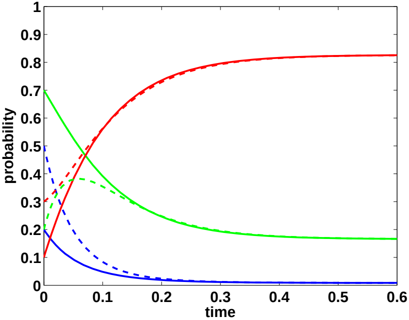


$\alpha = 10,\ \beta = 1$



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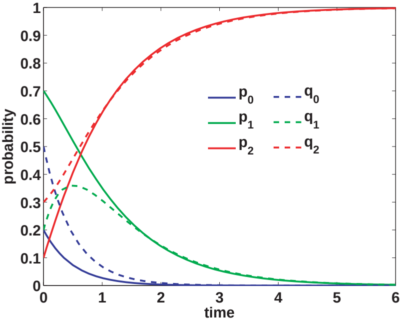

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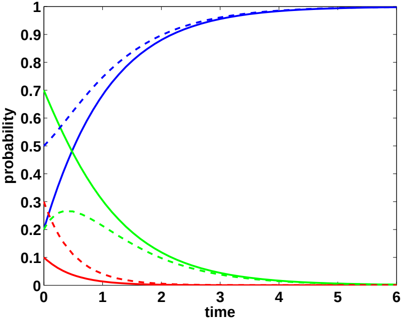

Eigenstructure of A when A is irreducible

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  - other eigenvalues of G have modulus less than γ
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- Therefore
  - 0 is simple eigenvalue of A
  - other eigenvalues of A have negative real part
  - $\ker(A)$ is one-dimensional, spanned by positive vector $\mathbf{v}$

Solutions of master equation when A is irreducible

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- Therefore $\mathbf{p}(t) \to \mathbf{v}_1$ for all initial conditions

Eigenstructure of A when A is reducible but not zero

$$A = \begin{bmatrix} 0 & \beta & 0 \\ 0 & -\beta & 2\beta \\ 0 & 0 & -2\beta \end{bmatrix}, \quad S_0 \overset{\beta}{\leftarrow} S_1 \overset{2\beta}{\leftarrow} S_2$$

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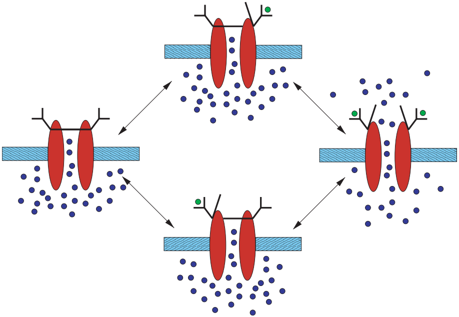
  hence $\mathbf{p}(t) \to (1, 0, 0)^T$ for all initial conditions
- Similarly, if $\beta = 0$ but $\alpha \neq 0$, then $\mathbf{p}(t) \to (0, 0, 1)^T$

Nonautonomous master equation



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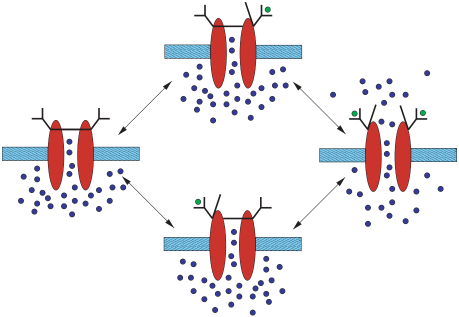

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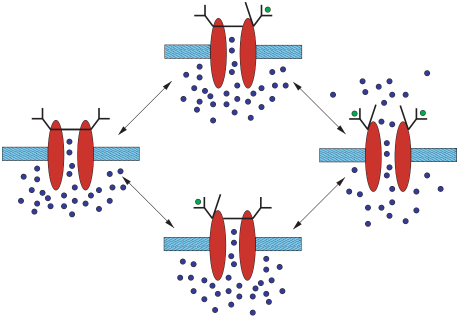

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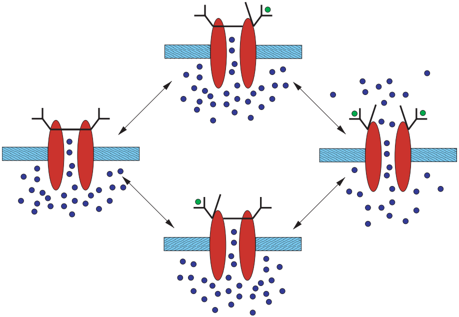

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  - α, β are functions of time
- How will solutions behave now?

Behavior of solutions of nonautonomous master equation

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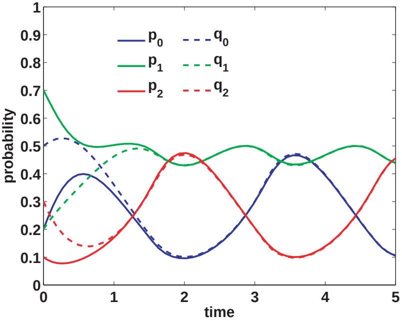
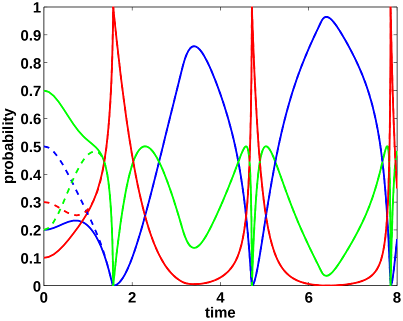
$\alpha = |\sin(t)|$, $\beta = |\cos(t)|$



$\alpha = |\tan(t)|$, $\beta = t$



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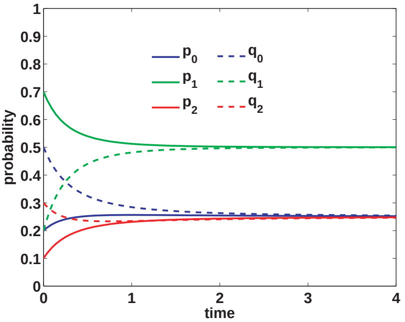
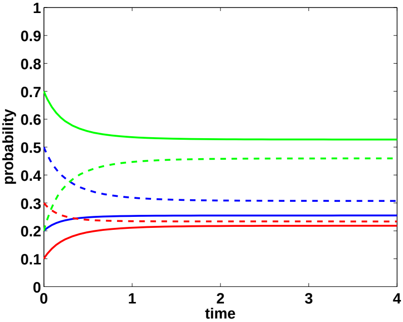
$\alpha = \beta = (t+1)^{-1}$



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



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$$a_{11}(t) = -1 - 9\cos^2(6t) + 12\sin(6t)\cos(6t)$$

$$a_{12}(t) = 12\cos^2(6t) + 9\sin(6t)\cos(6t)$$

$$a_{21}(t) = -12\sin^2(6t) + 9\sin(t)\cos(6t)$$

$$a_{22}(t) = -1 - 9\sin^2(6t) - 12\sin(6t)\cos(6t)$$

$A(t) = [a_{ij}(t)]$ 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 $\dot{\mathbf{x}} = A(t)\mathbf{x}$

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)

Outline for rest of talk

1. Set up the problem
2. Propose conjecture that characterizes large class of time-dependent A's for which probability distribution solutions of corresponding master equation are globally asymptotically stable (i.e. all such solutions approach each other in time)
3. Discuss van Kampen's theorem for autonomous master equations
4. Generalize van Kampen's theorem for nonautonomous master equations, and show that each generalization is special case of conjecture
5. Show that conjecture does not characterize all A's endowing probability distribution solutions of master equation with global asymptotic stability
6. Discuss existence of invariant manifolds

Derivation of master equation

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- Assuming transition probabilities are of the form

$$p(x_i, t + \Delta t|x_j, t) = a_{ij}(t)\Delta t + o(\Delta t) \quad (t \geq 0),$$

one derives *master equation* from CKE:

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

where off-diagonal entries are $a_{ij}(t) \geq 0$ and $a_{jj}(t) = -\sum_{i \neq j} a_{ij}(t)$

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  - van Kampen calls these $\mathbb{W}$-matrices

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- $\Sigma_1 = K \cap H_1$ is invariant

Global asymptotic stability

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

Definition

A probability distribution solution $\mathbf{p}$ of the master equation is *globally asymptotically stable* (GAS) in the set of all such solutions if for all other probability distribution solutions $\mathbf{q}$,

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

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- Note that $\mathbf{p}(t) - \mathbf{q}(t) \in H_0$ for all $t \geq 0$
- Therefore, master equation is GAS if and only if $\mathbf{0}$ is globally asymptotically stable in H_0

Conjecture

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

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Let $A : \mathbb{R}_+ \to \mathbb{R}^{n\times n}$ *be a continuous,* $\mathbb{W}$*-matrix-valued function, and let* $\lambda_1(t), \ldots, \lambda_n(t)$ *be an ordering of the n eigenvalues of* $A(t)$*, counting multiplicities, such that* $\Re(\lambda_1(t)) \geq \cdots \geq \Re(\lambda_n(t))$ *for all* $t \geq 0$*. If* $\Re(\lambda_2)$ *is not integrable, then the master equation is GAS.*

Eigenstructure of $\mathbb{W}$-matrices

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- Since column space of A is contained in H_0, algebraic and geometric multiplicities of 0 are equal
  - $A^k\mathbf{x} \neq \mathbf{v}$ for any $k \geq 1$, $\mathbf{x} \in \mathbb{R}^n$

Null space of $\mathbb{W}$-matrices

- Irreducible normal form: there exists permutation matrix P such that

$$P^{-1}MP = \begin{bmatrix} M_1 & N_{12} & \cdots & N_{1k} \\ 0 & M_2 & \cdots & N_{2k} \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & M_k \end{bmatrix}$$

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  - Otherwise, $\ker(M)$ has dimension $\geq 2 \Rightarrow \ker(M) \cap H_0$ is nontrivial

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- *splitting* if there exists permutation matrix P such that

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Conjecture revisited

Conjecture

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But eigenstructure can be misleading!

$||\mathbf{x}(t)||_1$ as Lyapunov function for H_0-solutions

- Recall $||\mathbf{x}||_1 = \sum_{i=1}^{n} |x_i| = \text{sgn}(\mathbf{x})^T \mathbf{x}$

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- If $\mathbf{x}(t)$ is H_0-solution of master equation, then $||\mathbf{x}(t)||_1$ is differentiable for a.e. t:

$$
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\frac{d||\mathbf{x}(t)||_1}{dt} &= \text{sgn}(\mathbf{x}(t))^T A(t)\mathbf{x}(t) \\
&= -\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)\left|x_j(t)\right| \\
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- $j \in I_+ \Leftrightarrow x_j(t) > 0$ and $j \in I_- \Leftrightarrow x_j(t) < 0 \Rightarrow \frac{d||\mathbf{x}(t)||_1}{dt} \leq 0$

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- If $\frac{d||\mathbf{x}(t)||_1}{dt} = 0$ then $A(t)$ is decomposable or splitting ($\Rightarrow \lambda_2(t) = 0$)
- The converse: if $\Re(\lambda_2(t)) < 0$ then $\frac{d||\mathbf{x}(t)||_1}{dt} < 0$

Conjecture rerevisited

Conjecture

Let $A : \mathbb{R}_+ \to \mathbb{R}^{n \times n}$ be a continuous, $\mathbb{W}$-matrix-valued function, and let $\lambda_1(t), \ldots, \lambda_n(t)$ be an ordering of the n eigenvalues of $A(t)$, counting multiplicities, such that $\Re(\lambda_1(t)) \geq \cdots \geq \Re(\lambda_n(t))$ for all $t \geq 0$. If $\Re(\lambda_2)$ is not integrable, then the master equation is GAS.

- If $\Re(\lambda_2(t)) < 0$ then $\frac{d||\mathbf{x}(t)||_1}{dt} < 0$ for any H_0-solution $\mathbf{x}$
- The nonintegrability of $\Re(\lambda_2)$ "should" ensure that $||\mathbf{x}(t)||_1 \to 0$

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.

Proof.

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  - $\Rightarrow \Re(\lambda_i) < 0 \quad (i = 2, \ldots, n)$
- Every probability distribution solution $\mathbf{p}$ of master equation is of form

$$\mathbf{p}(t) = \mathbf{v}_1 + c_2 e^{\lambda_2 t}\mathbf{v}_2 + \cdots + c_n e^{\lambda_n t}\mathbf{v}_n$$

where c_i's are polynomials in t of degree $< n$

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Proof.

- $\Re(\lambda_2) < 0$ since A is neither decomposable nor splitting
  - $\Rightarrow \Re(\lambda_i) < 0 \quad (i = 2, \ldots, n)$
- Every probability distribution solution $\mathbf{p}$ of master equation is of form

$$\mathbf{p}(t) = \mathbf{v}_1 + c_2 e^{\lambda_2 t}\mathbf{v}_2 + \cdots + c_n e^{\lambda_n t}\mathbf{v}_n$$

  where c_i's are polynomials in t of degree $< n$
- Therefore, $\mathbf{p}(t) \to \mathbf{v}_1$ independent of initial conditions

(Note: converse of theorem is also true) □

First generalization of van Kampen's theorem

- van Kampen's theorem is special case of conjecture
  - $\lambda_2(t) < 0$ is constant, so not integrable
  - all probability distribution solutions approach $\mathbf{v}_1$, so master equation is GAS

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  - $\lambda_2(t) < 0$ is constant, so not integrable
  - all probability distribution solutions approach $\mathbf{v}_1$, so master equation is GAS
- Theorem can be extended slightly using similar proof

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 master equation is GAS if and only if M is neither decomposable nor splitting and f is not integrable.

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Proof.

- fundamental matrix solution is

$$\Phi_s^t = \exp\left[\int_s^t A(u)du\right] = \exp\left[\left(\int_s^t f(u)du\right) M\right]$$

- Every probability distribution solution **p** is of form

$$\mathbf{p}(t) = \mathbf{v}_1 + c_2 e^{\mu_2 \int_0^t f(u)du}\mathbf{v}_2 + \cdots + c_n e^{\mu_n \int_0^t f(u)du}\mathbf{v}_n$$

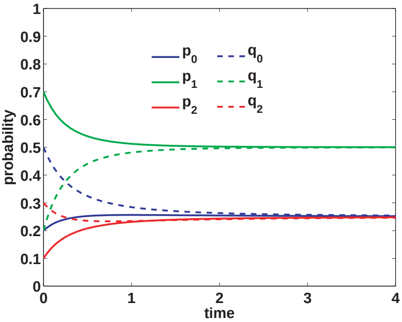
  where μ_i's are eigenvalues of M

- Therefore, $\mathbf{p}(t) \to \mathbf{v}_1$ if and only if $\int_0^t f(u)du \to \infty$

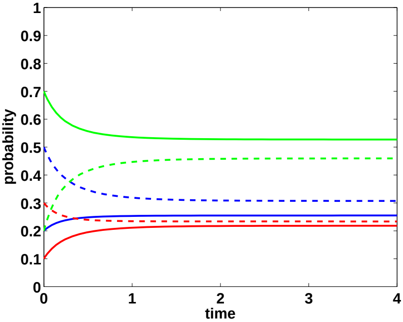
Example of first generalization

$$\frac{d\mathbf{p}}{dt} = A\mathbf{p} = f(t)\begin{bmatrix} -2 & 1 & 0 \\ 2 & -2 & 2 \\ 0 & 1 & -2 \end{bmatrix}\mathbf{p}$$

$f(t) = (t+1)^{-1}$



$f(t) = \exp(-2t)$



Generalization of van Kampen's theorem for periodic A

Theorem

If A is continuous, periodic, $\mathbb{W}$-matrix-valued function such that the ω-limit set of A contains at least one matrix which is neither decomposable nor splitting, then the master equation is GAS.

Proof.

□

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$$f : E \to \mathbb{R}_+, \quad f(\mathbf{y}) = ||\Phi_0^\tau \mathbf{y}||_1$$

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- Compactness of $E \Rightarrow f(\mathbf{z}) = \max\{f(\mathbf{y}) \mid \mathbf{y} \in E\}$ for some $\mathbf{z} \in E$
- Therefore, $||\Phi_0^{k\tau}\mathbf{x}||_1 \le f(\mathbf{z})^k ||\mathbf{x}||_1 \to 0$ as $k \to \infty$ for all $\mathbf{x} \in H_0$

Further generalization for asymptotically periodic A

Theorem

If A is continuous, $\mathbb{W}$-matrix-valued and 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

$$\lim_{t\to\infty} ||A(t) - B(t)||_1 = 0,$$

then the master equation is GAS.

- Theorem is special case of conjecture since λ_2 asymptotically approaches a nonpositive periodic function which is negative at least once during the period.

Another generalization of van Kampen's theorem

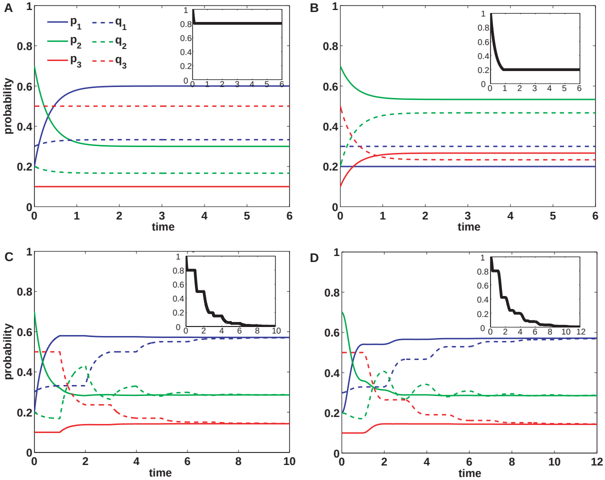
Theorem

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 the master equation is GAS.

- Proof is "involved", is (correct) extension of van Kampen's original method
- Idea: show that if $||\mathbf{x}(t)||_1 \to r > 0$, then $\omega(A)$ contains a decomposable or splitting matrix
- Theorem is special case of conjecture since $\omega(\lambda_2)$ contains negative number and $\lambda_2'(t)$ is bounded

$\lambda_2(t) = 0$ for all $t \geq 0$ but master equation is GAS

$$A(t) = \begin{cases} A_1, & t \in [0,1), \\ A_2, & t \in [1,2), \end{cases}, \quad A_1 = \begin{bmatrix} -1 & 1 & 0 \\ 1 & -1 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad A_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & -1 & 1 \\ 0 & 1 & -1 \end{bmatrix}$$



Low-dimensional invariant manifolds of Σ_1

- If master equation is GAS and $\Sigma \subseteq \Sigma_1$ is invariant manifold of master equation, then Σ is globally attracting (i.e. $\lim_{t\to\infty} \mathbf{p}(t) \in \overline{\Sigma}$)

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- In ion channel example, one-dimensional manifold $\mathcal{B}$ of all binomial distributions is invariant

$$\mathbf{b}(\theta) = \begin{bmatrix} (1-\theta)^2 \\ 2\theta(1-\theta) \\ \theta^2 \end{bmatrix} \quad (\theta \in [0,1])$$

meaning

$$A(t)\mathbf{b}(\theta) = \frac{d\mathbf{b}}{d\theta}\frac{d\theta}{dt} \quad \text{with} \quad \frac{d\theta}{dt} = \alpha(t)(1-\theta) - \beta(t)\theta$$

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- Last equation holds for *any* choice of nonnegative functions α, β

Thank you!

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