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Contributions to stochastic compartmental analysis

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Calcolo delle probabilità. — *Contributions to stochastic compartmental analysis* (*). Nota di VINCENZO CAPASSO e STEFANO L. PAVERI-FONTANA, presentata (**) dal Corrisp. G. SESTINI.

RIASSUNTO. — Viene affrontato lo studio della formalizzazione stocastica dei modelli compartimentali proposta da Matis e Hartley [5].

La risoluzione in forma chiusa per la funzione generatrice di probabilità (p.g.f.) mette in evidenza il ruolo dominante della matrice compartimentale nella evoluzione del sistema, il che consente di sfruttare sistematicamente risultati originati dalla corrispondente teoria deterministica.

Si ottiene una serie di implicazioni sul tipo di distribuzione probabilistica delle particelle nel sistema.

The equation

$$\frac{d}{dt}\,\boldsymbol{x}(t) = \mathbf{L}\boldsymbol{x}(t) + \boldsymbol{s}(t)\,, \qquad t > 0 \tag{1a}$$

$$\boldsymbol{x}(0) = \boldsymbol{x}^0 \in \mathbf{R}^{\mathrm{N}} \tag{1b}$$

is the representation of a linear *invariant* compartmental model [4], [7], [8] for the evolution of a given substance among N compartments within a biological system, iff:

a) $\mathbf{L} = (\mathrm{L}_{ik}) \in \mathbf{R}^{\mathrm{N}\times\mathrm{N}}$ is a compartmental matrix, namely

$$\mathrm{L}_{jk} \geq 0 \quad \text{for } j \neq k\,, \quad \text{and} \quad l_j^e \stackrel{\text{def}}{=} -\sum_{\substack{k=1\\k\neq j}}^{\mathrm{N}} \mathrm{L}_{kj} - \mathrm{L}_{jj} \geq 0 \quad \text{for } j \in \{1,\cdots,\mathrm{N}\}\,.$$

b) $\boldsymbol{x}^0 \geq 0$

c) $\boldsymbol{s}(t) \in \mathbf{R}^{\mathrm{N}}$, and $\boldsymbol{s}(t) \geq 0$ for $t \geq 0$.

Here $\mathbf{R}^{\mathrm{N}}$ denotes the set of N-dimensional real column vectors. In addition, for $\boldsymbol{v} \in \mathbf{R}^{\mathrm{N}}$, $\boldsymbol{v} > 0$ stands for $v_i > 0\,, i \in \{1,\cdots,\mathrm{N}\}$; $\boldsymbol{v} \geqq 0$ stands for $v_i \geqq 0$, $i \in \{1,\cdots,\mathrm{N}\}$; $\boldsymbol{v} \geq 0$ stands for $\boldsymbol{v} \geqq 0$, and $\boldsymbol{v} \neq \mathbf{0}$; a similar notation holds for matrices.

Moreover, $\mathbf{1} = (1\,,1\,,\cdots,1)^{\mathrm{T}} \in \mathbf{R}^{\mathrm{N}}$; $\boldsymbol{e}^1 = (1\,,0\,,\cdots,0)^{\mathrm{T}} \in \mathbf{R}^{\mathrm{N}}$, $\boldsymbol{e}^2 = (0\,,1\,,0\,,\cdots,0)^{\mathrm{T}} \in \mathbf{R}^{\mathrm{N}}$, etc. Finally, if $\boldsymbol{v} \in \mathbf{R}^{\mathrm{N}}$, $\mathrm{diag}(\boldsymbol{v}) = (\delta_{ik}\, v_k) \in \mathbf{R}^{\mathrm{N}\times\mathrm{N}}$ where $\delta_{ik} = 0$ for $i \neq k$, $\delta_{ik} = 1$ for $i = k$.

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In Eqs. (1), $x_k(t)$ is the expected value of the number of molecules of the substance in compartment k at time t; $s_k(t)$ is the injection rate of the substance into compartment k at time t; $l_k^e x_k(t)$ is the leaking rate from compartment k to the external world at time t; $\mathbf{L}$ is closed (or leakless) iff $l_k^e = 0$ for $k \in \{1, \cdots, N\}$.

The solution of Cauchy problem (1) is

$$x(t, x^0, s(\cdot)) = e^{\mathbf{L}t} x^0 + \int_0^t (\exp \mathbf{L}(t-\tau))\, s(\tau)\, d\tau . \tag{2}$$

In the literature (see for example [3]) one may find the following results. They concern the transition matrix $\exp(\mathbf{L}t)$, and, for all of them, physical interpretations in terms of leakages, flows, etc. can be given.

PROPOSITION 1. *Let* $\mathbf{L} \in \mathbf{R}^{N \times N}$ *be compartmental. Then*

a)
$$\exp(\mathbf{L}t) \geq 0$$

and

$$0 \leqq [\exp(\mathbf{L}t)]_{ik} \leqq 1 \qquad \textit{for} \quad i, k \in \{1, \cdots, N\}, \qquad t \geqq 0 ;$$

b) *if* $\mathbf{L}$ *is irriducible, then* $\exp(\mathbf{L}t) > 0$ *for* $t > 0$;

c) *if* $\mathbf{L}$ *is closed, then* $\mathbf{L}$ *is singular*

and

$$\exp(\mathbf{L}^T t)\, \mathbf{1} = \mathbf{1} \qquad \textit{for} \quad t \geqq 0 ;$$

d) *if* $\mathbf{L}$ *is irreducible, then it is closed iff it is singular*;

e) *if* $\mathbf{L}$ *is irreducible and closed then a (Perròn) vector* $p > 0$ *with* $\mathbf{1}^T p = 1$ *exists such that* $\exp(\mathbf{L}t) \to p\mathbf{1}^T$ *for* $t \to +\infty$.

In the literature (see, e.g., [2], [5], [6]) the problem

$$\begin{aligned} \frac{d}{dt} P(n; r) = {} & \sum_{i=1}^{N} \sum_{\substack{k=1 \\ k \neq 1}}^{N} L_{ik} ((n_k + 1) P(n + e^k - e^i; t) - n_k P(n; t)) + \\ & + \sum_{k=1}^{N} l_k^e ((n_k + 1) P(n + e^k; t) - n_k P(n; t)) + \\ & + \sum_{k=1}^{N} s_k(t) (P(n - e^k; t) - P(n; t)), \qquad t > 0, \end{aligned} \tag{3a}$$

subject to the initial conditions

$$P(n; 0) = P^0(n), \qquad n \in \mathbf{N}^N, \tag{3b}$$

and to the further requirements

(3c) $$0 \leqq \mathrm{P}(\boldsymbol{n};t) \leqq 1\,, \qquad \boldsymbol{n} \in \mathbf{N}^{\mathrm{N}}\,, \qquad t \geqq 0\,,$$

(3d) $$\sum_{\boldsymbol{n}\in\mathbf{N}^{\mathrm{N}}} \mathrm{P}(\boldsymbol{n};t) = 1\,, \qquad t \geqq 0\,,$$

has been proposed as the stochastic counterpart of problem (1).

Here, $\mathrm{P}(\boldsymbol{n};t) = \mathrm{Prob}(\tilde{\boldsymbol{n}}(t) = \boldsymbol{n})$, $\tilde{\boldsymbol{n}}(t) = (\tilde{n}_1(t), \cdots, \tilde{n}_{\mathrm{N}}(t))^{\mathrm{T}} \in \mathbf{N}^{\mathrm{N}}$, (with $\mathbf{N} = \{0, 1, 2, \cdots\}$); finally for any $k \in \{1, \cdots, \mathrm{N}\}$, $\tilde{n}_k(t)$ is the random variable which indicates the number of molecules of the substance which are present in compartment k at time t.

It can be shown [1] that if the initial distribution, $\{\mathrm{P}^0(\boldsymbol{n}), \boldsymbol{n} \in \mathbf{N}^{\mathrm{N}}\}$, is such that the expected values

$$x_k(0) = \mathrm{E}[\tilde{n}_k(0)] = \sum_{\boldsymbol{n}\in\mathbf{N}^{\mathrm{N}}} n_k \mathrm{P}^0(\boldsymbol{n})$$

exist and are finite, then a unique solution, $\{\mathrm{P}(\boldsymbol{n};t), \boldsymbol{n} \in \mathbf{N}^{\mathrm{N}}\}$, of problem (3) exists at any time $t \geqq 0$.

The probability generating function (p.g.f.) of the random vector $\tilde{\boldsymbol{n}}(t)$ is

(4) $$\mathrm{G}(\xi;t) = \sum_{\boldsymbol{n}\in\mathbf{N}^{\mathrm{N}}} \prod_{i=1}^{\mathrm{N}} \xi_i^{n_i} \mathrm{P}(\boldsymbol{n};t)$$

(with $\xi \in \mathbf{C}^{\mathrm{N}}$ such that $|\xi_i| \leq 1$ for $i \in \{1, \cdots, \mathrm{N}\}$).

We find that it obeys the evolution problem

(5a) $$\frac{\partial}{\partial t}\mathrm{G}(\xi;t) = (\xi - \mathbf{1})^{\mathrm{T}}\left(\mathbf{L}\frac{\partial}{\partial\xi} + \boldsymbol{s}(t)\right)\mathrm{G}(\xi;t)\,; \qquad t > 0\,,$$

(5b) $$\mathrm{G}(\xi;0) = \mathrm{G}^0(\xi)\,.$$

whose solution is

(6) $$\mathrm{G}(\xi;t) = \exp\left((\xi - 1)^{\mathrm{T}}\int_0^t (\exp(\mathbf{L}\tau))\,\boldsymbol{s}(t-\tau)\,\mathrm{d}\tau\right)\times$$
$$\times\,\mathrm{G}^0((\exp(\mathbf{L}^{\mathrm{T}}t))(\xi - \mathbf{1}) + \mathbf{1})\,.$$

If $\mathbf{L}$ is closed (see part c of Prop. 1) then result (6) reduces to

(7) $$\mathrm{G}(\xi;t) = \exp\left((\xi - \mathbf{1})^{\mathrm{T}}\int_0^t (\exp(\mathbf{L}\tau))\,\boldsymbol{s}(t-\tau)\,\mathrm{d}\tau\right)\times\mathrm{G}^0((\exp(\mathrm{L}^{\mathrm{T}}t)(\xi)\,.$$

A direct consequence of Eq. (7) is the following: if

$$x^0 = \mathrm{E}\,[\tilde{n}\,(0)] = \sum_{n \in \mathbf{N}^N} n\mathrm{P}^0\,(n) = \left(\frac{\partial}{\partial \xi}\,\mathrm{G}^0\,(\xi)\right)_{\xi=\mathbf{1}}, \tag{8}$$

then

$$x\,(t) = \mathrm{E}\,[\tilde{n}\,(t)] = x\,(t\,,\,x^0,\,s\,(\cdot))\,. \tag{9}$$

Hence, the comparison of Eqs. (9) and (2) shows that the evolution of the expected values according to the stochastic model (3) is in agreement with the corresponding evolution according to the deterministic model (1).

Results which are strictly related to Eq. (6) have already appeared in the literature (see, e.g. [2], [5], [6] and other papers by the same Authors). Eq. (6) summarizes them and casts them in a more compact form.

Indeed by inspection of (6) one can recognize that the evolution matrix, $\exp\,(\mathbf{L}t)$, plays for the stochastic process a role which is as important as the one which it plays for the deterministic process (Eq. 2). Hence form (6) permits to transfer to the stochastic problem a large part of the information which has been established, concerning $\exp\,(\mathbf{L}t)$, in the deterministic compartmental literature.

As a consequence of Eq. (6) we are now in a position to draw several implications, a part of which have appeared in the literature for specific cases.

REMARK 1. Let $\tilde{n}_0\,(t)$ denote the random vector which describes the number of particles which were present in the compartments at time 0 and are still present at time t. Let $\tilde{n}_s\,(t)$ denote the random vector which describes the number of particles which arrived from the sources into the compartments in $]0\,,t]$ and are still present at time t. Due to be basic hypothesis of the stochastic process, according to which particles in the system act independently of each other, $\tilde{n}_0\,(t)$ and $\tilde{n}_s\,(t)$ are independent random vectors, at any time $t \geq 0$.

The p.g.f. of $\tilde{n}_0\,(t)$ is given by

$$\mathrm{G}_0\,(\xi\,;t) = \mathrm{G}^0\,[(\exp\,(\mathbf{L}^{\mathrm{T}}\,t))\,(\xi - \mathbf{1}) + \mathbf{1}]\,,$$

while the p.g.f. of $\tilde{n}_s\,(t)$ is given by

$$\mathrm{G}_s\,(\xi\,;t) = \exp\,[(\xi - \mathbf{1})^{\mathrm{T}}\,x\,(t\,,0\,;s\,(\cdot))]\,.$$

Then as a consequence of Eq. (6) the p.g.f. of

$$\tilde{n}\,(t) = \tilde{n}_0\,(t) + \tilde{n}_s\,(t)$$

is given by

$$\mathrm{G}\,(\xi\,;t) = \mathrm{G}_0\,(\xi\,;t)\,\mathrm{G}_s\,(\xi\,;t)\,.$$

REMARK 2. If $\tilde{\boldsymbol{n}}(0)$ is a multivariate Poisson random vector with independent components; i.e. if

$$G^0(\xi) = \exp[(\xi - \mathbf{1})^T \boldsymbol{x}^0],$$

then

$$G(\xi; t) = \exp[(\xi - \mathbf{1})^T \boldsymbol{x}(t, \boldsymbol{x}^0, \boldsymbol{s}(\cdot))], \qquad t \geqq 0,$$

which in turn is the p.g.f. of a multivariate Poisson random vector with independent components.

REMARK 3. If the system has sources and at time zero is completely empty, i.e. if the initial p.g.f. is

$$G^0(\xi) = 1,$$

then

$$G(\xi; t) = \exp[(\xi - \mathbf{1})^T \boldsymbol{x}(t, \mathbf{0}, \boldsymbol{s}(\cdot))], \qquad t \geqq 0.$$

Hence $\tilde{\boldsymbol{n}}(t)$ is at any time $t \geqq 0$ a multivariate Poisson random vector with independent components.

REMARK 4. If initially (with certainty) $\tilde{\boldsymbol{n}}(0) = \overset{0}{n}_k \boldsymbol{e}^k$ (for some $k \in \{1, 2, \cdots, N\}$), and if there are no sources, i.e. if the initial p.g.f. is given by $G^0(\xi) = \xi_k^{\overset{0}{n}_k}$, then

$$G(\xi; t) = \left[\sum_{j=1}^{N} p_{kj}(t)\, \xi_j + p_{k0}(t)\right]^{\overset{0}{n}_k}, \qquad t \geqq 0,$$

where

$$p_{kj}(t) = (\exp(\mathbf{L}^T t))_{kj}, \qquad j \in \{1, \cdots, N\},$$

and

$$p_{k0}(t) = 1 - \sum_{j=1}^{N} p_{kj}(t).$$

Hence $\tilde{\boldsymbol{n}}(t)$ has a multinomial distribution with parameters $\overset{0}{n}_k$, p_{kj} and p_{k0}. If the system is closed, since $(\exp(\mathbf{L}^T t))\, \mathbf{1} = \mathbf{1}$ we have

$$\sum_{j=1}^{N} (e^{\mathbf{L}^T t})_{kj} = 1 \qquad \text{and} \quad p_{k0}(t) = 0$$

at any time $t \geqq 0$.

REMARK 5. If initially we have (with certainty) for any $k \in \{1, \cdots, N\}$, $\overset{0}{n}_k$ particles in the k-th compartment and there are no sources, i.e. if the initial p.g.f. is given by

$$G^0(\xi) = \prod_{k=1}^{N} \xi_k^{\overset{0}{n}_k},$$

then

$$G(\xi ; t) = \prod_{k=1}^{N} \left[\sum_{j=1}^{N} p_{kj}(t)\, \xi_j + p_{k0}(t) \right]^{n_k^0} .$$

Due to the fact that the particles in the system act independently of each other, we can state that in this case $\tilde{\boldsymbol{n}}(t)$ is the sum of N independent random vectors:

$$\tilde{\boldsymbol{n}}(t) = \sum_{k=1}^{N} \tilde{\boldsymbol{n}}^{(k)}(t) ,$$

where any $\tilde{\boldsymbol{n}}^{(k)}(t)$ is a multinomial random vector with parameters n_k^0 , $p_{kj}(t)$ and $p_{k0}(t)$ (see Remark 4).

REMARK 6. If the system is closed and irriducible, without sources, and if it initially contains (with certainty) M particles (globally), then

$$\lim_{t \to +\infty} G(\xi ; t) = (\boldsymbol{p}^{T} \xi)^{M} ,$$

where $\boldsymbol{p}$ is the Perron vector.

Hence for long times G approaches the p.g.f. of a multinomial random vector with parameters M and $p_1, \cdots, p_N$ (the components of the Perron vector $\boldsymbol{p}$).

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