Solving random differential equations using Louville equation.

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Motivation

The quantification of uncertainty in dynamic models is currently playing an important role in many applied areas. Classical deterministic differential equations, which have demonstrated to be powerful tools for analysing problems that appear in areas such as Physics, Engineering, Chemistry, Epidemiology, etc., need to consider randomness in their formulation in order to account for measurement errors and inherent complexity of problems under study. It has motivated the development of two main classes of differential equations dealing with uncertainty, namely, random differential equations (r.d.e.'s) and stochastic differential equations (s.d.e.'s). R.d.e.'s are those in which random effects are directly manifested in its inputs parameters (initial/boundary conditions, source term and coefficients). These inputs are assumed to satisfy regularity properties such as continuity, differentiability, etc., in some adequate stochastic sense such as mean square calculus (see [1]). A major advantage of considering r.d.e.'s is that a wide range of probabilistic distributions can be assigned to its inputs including Exponential, Gaussian, Beta, etc, distributions. As a consequence, r.d.e.'s provide great flexibility in dealing with real models.

R.d.e.'s and the Liouville-Gibbs equation

Let us consider the following initial value problem (IVP):

$$\begin{cases} \mathbf{Y}'(t) = \mathbf{F}(t, \mathbf{Y}(t)), & t > t_0, \\ \mathbf{Y}(t_0) = \mathbf{Y}_0, \end{cases} \tag{1}$$

where $\mathbf{F} = (F_1, \dots, F_n) : I \times \mathbb{R}^n \longrightarrow \mathbb{R}^n$ is a deterministic $C^1(I \times \mathbb{R}^n)$ function, $I \subset \mathbb{R}$ is a non-trivial interval, with $t_0 \in I$, $\mathbf{Y}(t) = (Y_1(t), \dots, Y_n(t))$ and $\mathbf{Y}_0$ is a random variable with a known PDF $p_0(\mathbf{y})$. Also the derivative is considered in the m.s. sense (see [Ch. 4, 1]). The characteristic function of the stochastic process $\mathbf{Y}(t)$ for a fixed time t is

$$\phi(t, \mathbf{u}) = \mathbb{E}\left[e^{i\mathbf{u}^T\mathbf{Y}(t)}\right] = \mathbb{E}\left[e^{i\sum_{k=1}^n u_k Y_k(t)}\right] = \int_{\mathbb{R}^n} e^{i\mathbf{u}^T\mathbf{y}} p(t, \mathbf{y}) \mathrm{d}\mathbf{y},$$

where $p(t, \mathbf{y})$ denotes th first probability density function (1-PDF) of $Y(t)$. Now, let us calculate the partial derivative $\frac{\partial \phi_{\mathbf{Y}(t)}}{\partial t}(t, u)$ in two different ways. On the one hand, using that m.s. limits and the expectation operator commute ([1, Thm. 4.2.1])

$$\frac{\partial \phi(t, \mathbf{u})}{\partial t} = \frac{\partial}{\partial t}\mathbb{E}\left[e^{i\sum_{k=1}^n u_k Y_k(t)}\right] = \mathbb{E}\left[i\sum_{k=1}^n u_k Y_k'(t) e^{i\mathbf{u}^T\mathbf{Y}(t)}\right] = i\sum_{k=1}^n u_k \mathbb{E}[Y_k'(t) e^{i\mathbf{u}^T\mathbf{Y}(t)}]$$

$$= i\sum_{k=1}^n u_k \mathbb{E}[F_k(t, \mathbf{Y}(t)) e^{i\mathbf{u}^T\mathbf{Y}(t)}] = i\sum_{k=1}^n u_k \int_{\mathbb{R}^n} e^{i\mathbf{u}^T\mathbf{y}} F_k(t, \mathbf{y}) p(t, \mathbf{y}) \mathrm{d}\mathbf{y}.$$

Using the linearity of the Fourier transform,

$$\frac{\partial \phi(t, \mathbf{u})}{\partial t} = \mathcal{F}\left[-\sum_{k=1}^n \frac{\partial}{\partial y_k}(F_k(t, \mathbf{y}) p(t, \mathbf{y}))\right](\mathbf{u}), \tag{2}$$

where $\mathcal{F}$ is the Fourier transform for $\mathrm{L}^1(\mathbb{R})$ functions.

On the other hand, using differentiation under the integral sign we get

$$\frac{\partial \phi(t, \mathbf{u})}{\partial t} = \int_{\mathbb{R}^n} e^{i\mathbf{u}^T\mathbf{y}} \frac{\partial p(t, \mathbf{y})}{\partial t} \mathrm{d}\mathbf{y} = \mathcal{F}\left[\frac{\partial p(t, \mathbf{y})}{\partial t}\right](\mathbf{u}). \tag{3}$$

Finally, using the inverse Fourier transform, we obtain the Liouville-Gibbs equation

$$\frac{\partial p(t, \mathbf{y})}{\partial t} + \sum_{k=1}^n \frac{\partial}{\partial y_k}(F_k(t, \mathbf{y}) p(t, \mathbf{y})) = 0. \tag{4}$$

This equation can be written in terms of the divergence operator using as initial condition the PDF of $\mathbf{Y}_0$, which is assumed to be known:

$$\begin{cases} \dfrac{\partial p(t, \mathbf{y})}{\partial t} + \displaystyle\sum_{k=1}^n F_k(t, \mathbf{y}) \frac{\partial p(t, \mathbf{y})}{\partial y_k} = -p(t, \mathbf{y}) \nabla_{\mathbf{y}} \cdot \mathbf{F}(t, \mathbf{y}), & t > 0, \\ p(0, \mathbf{y}) = p_0(\mathbf{y}), \quad \forall \mathbf{y} \in S_0, \end{cases} \tag{5}$$

where S_0 denotes the interior of the support of p_0 which we will suppose is a smooth hypersurface.

It can be proved that this IVP has a unique solution ([2, Thm. 1.10]). Furthermore, using the method of characteristics we can find its analytical solution, which is, using the notation in [1, Eq. 6.60], the following

$$p(t, \mathbf{y}) = \left(p_0(\mathbf{y}_0) \exp\left\{-\int_{t_0}^t \nabla_{\mathbf{y}} \cdot \mathbf{F}(\tau, \mathbf{y} = h(\tau, \mathbf{y}_0)) \mathrm{d}\tau\right\}\right)\Big|_{\mathbf{y}_0 = h^{-1}(t, \mathbf{y})}. \tag{6}$$

That is, by solving the IVP (1), we obtain a solution given by $\mathbf{Y}(t) = h(t, \mathbf{Y}_0)$. Solving this last equation for $\mathbf{Y}_0$ gives an expression $\mathbf{Y}_0 = h^{-1}(t, \mathbf{Y})$, which is what we use in the equation (6).

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References

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The Gompertz model

We will apply this method to solve the randomized Gompertz model used to study the time evolution of cancer cells, given by the following IVP

$$\begin{cases} N'(t) = N(t)[C - B\ln(N(t))], \ t > 0, \\ N(t_0) = N_0, \end{cases} \tag{7}$$

where $N_0, B, C > 0$ are random variables whose joint PDF $p_0(n_0, b, c)$ is assumed known. The random variable N_0 denotes the size of the tumor in cm^3, B represents the cell division rate and $C = B - \mu_p > 0$ represents the difference between the cell division rate (B) y and the cell death rate (μ_p). Its corresponding Liouville-Gibbs equation is the following

$$\begin{cases} \dfrac{\partial p(t, n, b, c)}{\partial t} + \dfrac{\partial(n[c - b\ln(n)]p(t, n, b, c))}{\partial n} = 0, \ \forall t > t_0, \\ p(t_0, n, b, c) = p_0(n, b, c). \end{cases} \tag{8}$$

And its solution is

$$p(t, n) = \int_{\mathbb{R}}\int_{\mathbb{R}} p_{N_0}(n^{e^{b(t-t_0)}} e^{-c/b(e^{b(t-t_0)}-1)}) p_B(b) p_C(c) e^{\eta(t,n,b,c)} \mathrm{d}b\mathrm{d}c.$$

where

$$\eta(t, n, b, c) = b(t - t_0) + \frac{c}{b}\left(e^{b(t-t_0)} - 1\right) + cte^{b(t-t_0)}$$
$$- \left(e^{b(-t+t_0)}(1 + bt) - 1\right)\ln\left[e^{-\frac{c\left(-1+e^{b(t-t_0)}\right)}{b}} n^{e^{b(t-t_0)}}\right]$$
$$+ bt\ln\left[e^{-\frac{c\left(-1+e^{b(-t+t_0)}\right)}{b}}\left(e^{-\frac{c\left(-1+e^{b(t-t_0)}\right)}{b}} n^{e^{b(t-t_0)}}\right)^{e^{b(-t+t_0)}}\right].$$

Now, we will show the graphical output of a numerical simulation of the Gompertz model using the following parameters:

- We consider N_0 as a normal distribution truncated in the [0,1] interval with $\mu = 0.0035, \sigma = 0.001$.
- For B, C we use the following uniform distributions: $B \sim \mathrm{Un}[0.12, 0.13]$ and $C \sim \mathrm{Un}[0, 0.003]$.

In Figure 1 we can see the 1-PDF of the solution stochastic process in three different values of t, measured in days.

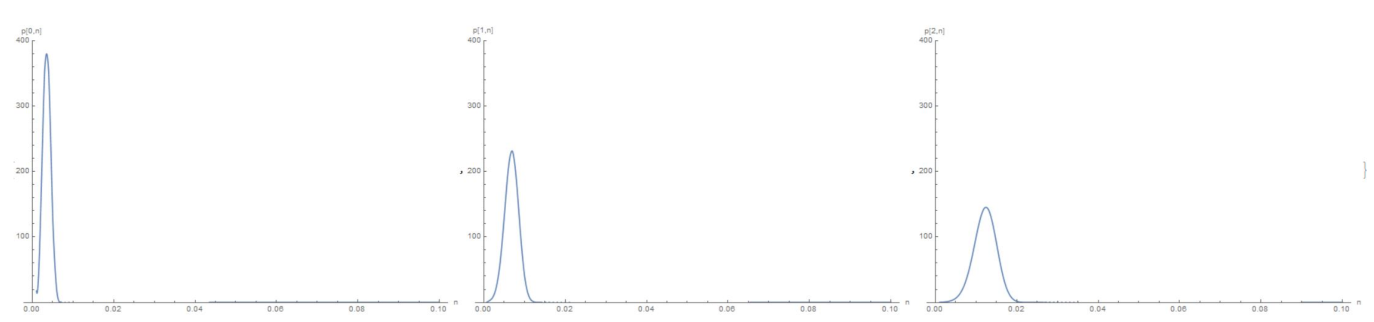

Fig. 1: Left: $t = 0$, Middle: $t = 1$ and Right: $t = 2$.

Figure 2 shows the mean of the solution stochastic process with a 95% confidence interval.

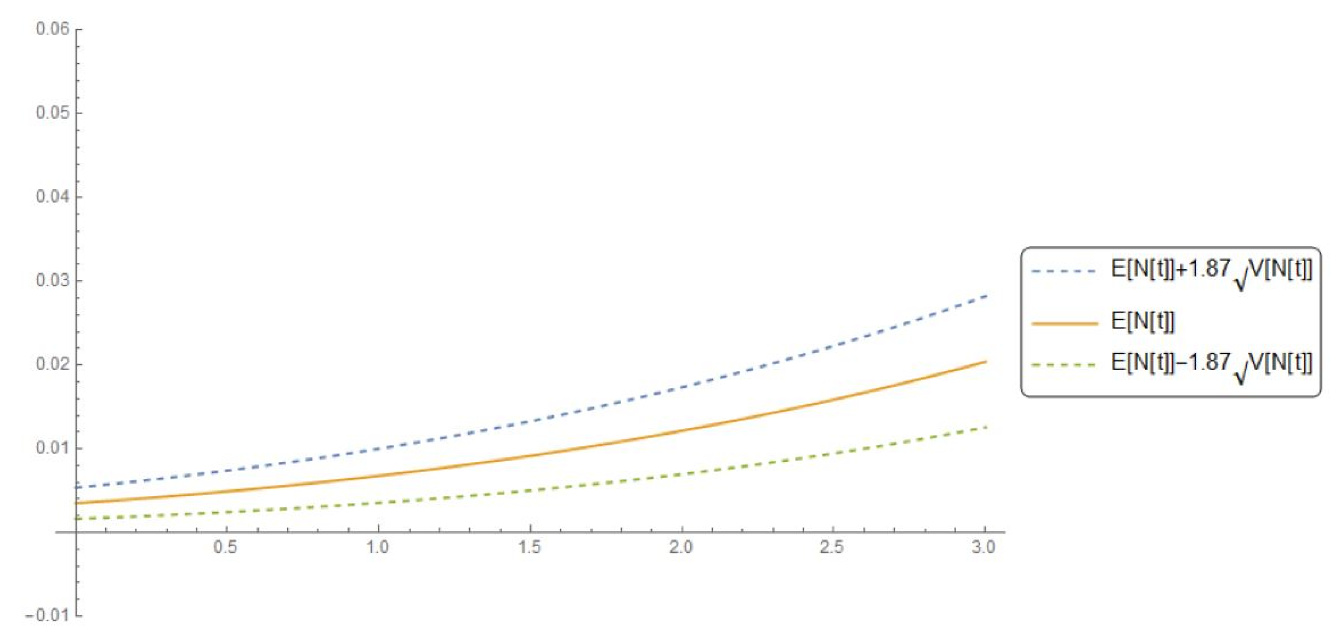

Fig. 2: Simulation of the mean (solid line) and a 95% confidence intrval (dashed lines) for the Gompertz model.