Dynamic modelling of food nutrients/contaminant exposure : an overview

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Outline

Evaluation of global exposure to some nutrients/food contaminants

How to evaluate the global exposure U of a population to some nutrients (fat/suggar,alt) or specific contaminants (chemical risks) in food?

- Food contains contaminants which may be harmfull to the body : natural contaminants (mycotoxins : Ochratoxin, aflatoxin, cyclochlorotin, lutéoskirin, "The natural is often harmful"), polluants (dioxines, pesticides, NH3, NOx, SO2, CO), heavy metals (Pb, Cadmium, , Mercury, Cyanure, arsenic), additives, etc.
- On the contrary, nutrients in food are essential to the body but should not be too high (for example : suggar, fat, salt, transformed food)
- Here bacterial and epidemiological aspects not under study (Campylobacter, Salmonella, Listeria etc...).

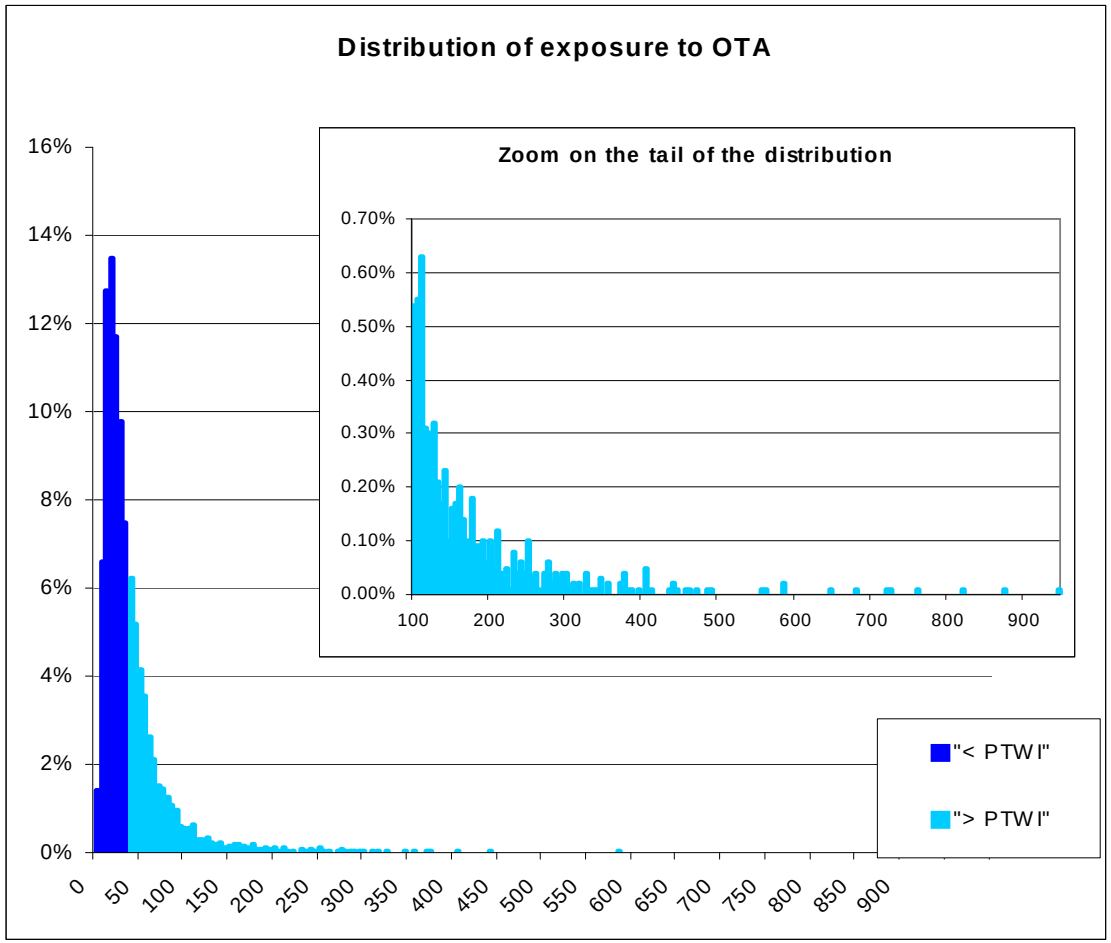
The static approach

U= global exposure to a contaminant/nutrient, generally not observable directly= sums of products of contamination doses/nutrient composition, K, with consumed quantities Q
PTWI = Provisional tolerable weekly intake, calculated from experiences on animal (with a protective factor). Medical parameter.

- Parameter of interest $\theta = P(U > PTWI)$
- Three sources of data
  - Consumption data from French surveys (Q individual food consumption (per body weights) or household (purchase on long period), INCA 1999 (AFSSA), SECODIP Panels, INCA2 (Anses)
  - Contamination data (K): analytical surveys on several food items from different French institutions (DGCCRF, DGAL, Ifremer etc.). Does not cover all products... Biais.
  - Nutrients : composition tables : Ciqual (ANSES), FAO/INFOODS with specific references to some continents. In general only 43 nutrients are considered in France.

What is done at the European level and international level (OMS)?

- Quantify global food exposure U of the whole population to a given contaminant, on a given period a week or a year, by combining the three sources of information
- Mean calculus: use of contamination means (or equivalently nutrients composition), to transform consumptions into contaminants (or nutrients. Non parametric/ parametric evaluation of the distribution of the global contamination U .
- Specific problems due to the analytical data at hand (left trucation due the lower limit of detection for contaminants)



Fat tails and strong disymetry

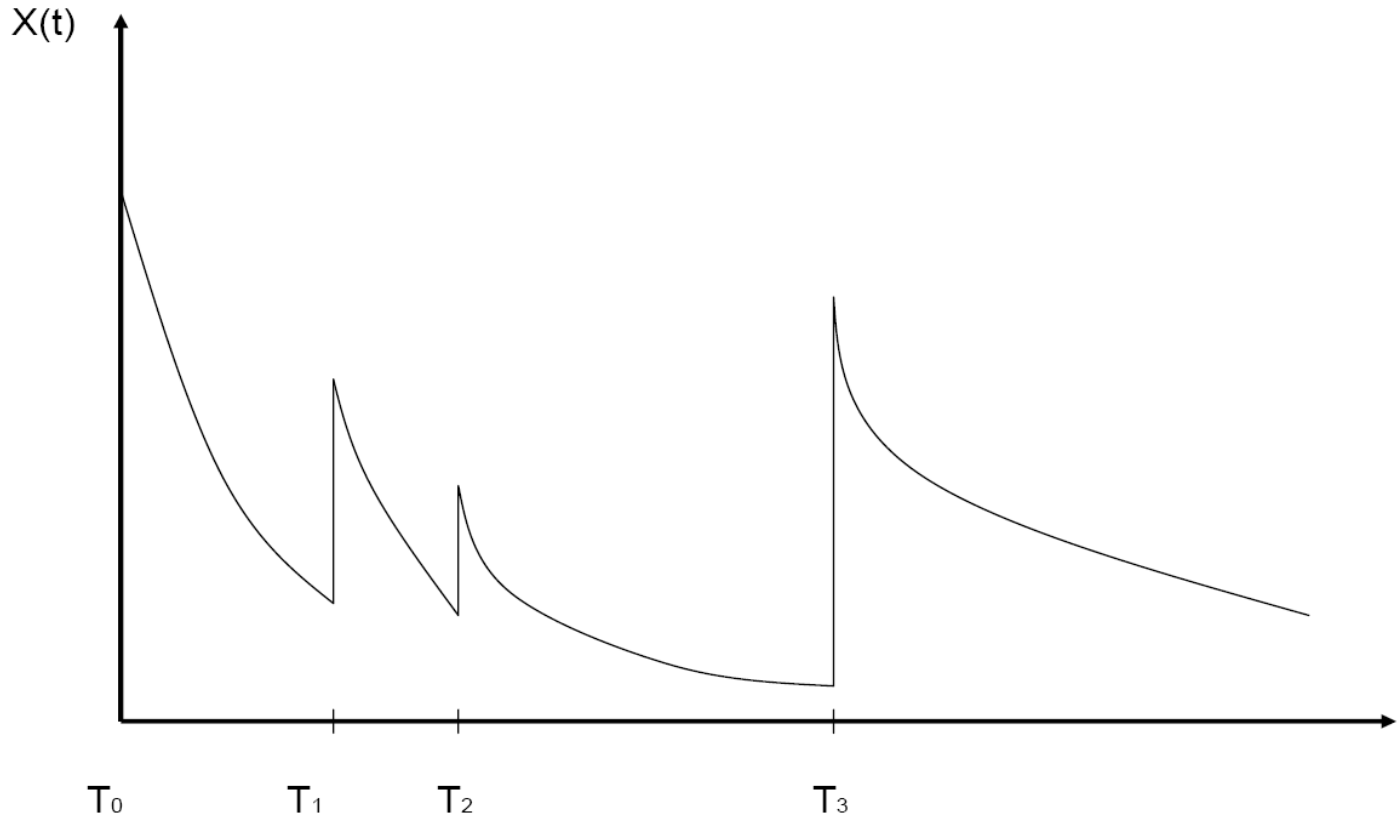
Most Political decision based on this static approach

- Transform 3 main nutrients (fat, suggar, salt)/calories into a mean score : FSA (Food standard Agency used in great Britain)-> largest=worst. FSA splitted into 5 categories -> Nutriscore (very normative approach)
- Used Models : comparison of means in moderate dimensions , double differences models: Dubois et al (2020), Gary L. Lilien ISMS-MSI-EMAC Practice Price 2023.
- Modeling the tail index of a Generalized Pareto distribution, conditionally to some explanatory variables (age, regions,income, profession,...)
- $\gamma(X) = h(X'\beta)$

Toward a dynamic approach of contaminant risk exposure

- Need to take into account nutrients, transformed food, additives, contaminants, etc...
- Need to take into account the dynamic of consumption **(Economic and sociological behaviour)**, also very important for political issues (fat-tax, contaminants taxes,nutritional logos)
- Need to take into account the phamaco-kinetic behaviour of the contaminant in the body (natural elimination) **(biological parameters)**
- Eventually take into account the assimilation phenomenon and elimination due to sport.

A simple ruin model : KDEM, Bertail, Clémençon, Tressou(2008),(2011)



A variant of a ruin model with a natural barrier at 0 : "'ruin" occurs when we cross a level PTWI. Severity of the "ruin" indicated by some indicators like "time over the threshold PTWI" area of the curve (process) over the threshold etc.

Some notations

List of P types of possibly contaminated food, indexed by $p = 1, \ldots, P$,
Exposure U, with probability distribution $F_{\mathcal{U}}$ with density f_U
$Q = (Q^{(1)}, \ldots, Q^{(P)}$: consumption of food of type p, normalized by the body weight with distribution $F_{\mathcal{Q}}$
$K = (K^{(1)}, \ldots, K^{(P)})$, contamination ratio vector drawn from some distribution $F_{\mathcal{K}} = \otimes_{p=1}^{P} F_{\mathcal{K}^{(p)}}$
Global exposure given by

$$U = \langle K, Q \rangle$$

A Piecewise Deterministic Markov Process

- $T_0 = 0$
- T_n dates of contaminated meals
- **Marks** $U_n = \langle K_n, Q_n \rangle$
- $(T_n, Q_n)_{n \geq 1}$ describing dietary behavior is assumed independent from the sequence (K_n),
- $Q_i, , i = 1, ..., n, ...$ independent
- Inter-intake times $\Delta T_{n+1} = T_{n+1} - T_n, n \geq 1$, i.i.d. r.v.'s with common probability distribution $G(dt) = g(t)dt$ and $m_G = \int_{t=0}^{\infty} tG(dt) < \infty$

Pharmacokinetic elimination between intakes

Elimination/excretion of the chemical in between intakes is described by a differential equation (see Gibaldi and Perrier, 1992)

$$\frac{dx}{dt}(t) = \theta \times x(t), \tag{2.1}$$

where θ in Θ, the elimination parameter is eventually random.

The *half-life* of the chemical in the body, $log(2)/\theta$, that is the time required for the total body burden x to decrease by half in absence of new intake

Model a bit too restrictive for some contaminants and does not allow for an absorption phase in the body. Moreover does not take into account for the compartments phenomenon : contaminants at stocked at different communicating places in the body.

More generally, assume that the elimination is driven by a differential equation

$$\dot{x}(t) = -r(x(t), \theta)$$

$r(x, \theta)$ strictly positive and continuous on $\mathbb{R}_+^* \times \Theta$, such that for all $\theta \in \Theta$, $r(0, \theta) = 0$ for all $(\epsilon, \theta) \in (0, 1) \times \Theta$:

$$inf_{\epsilon < x < \epsilon^{-1}} r(x, \theta) > 0 \text{ and } sup_{0 < x < \epsilon^{-1}} r(x, \theta) < \infty.$$

Particular case : $r(x, \theta) = \theta x$ exponential elimination.
In the following θ will be assumed to be random with distribution H, on a set $\Theta \subset \mathbb{R}^d$.

The cumulative process in the body : piecewise deterministic jump model

Cumulative contamination intakes $B(t) = \sum_{n=1}^{N(t)} U_n$ with $U_n = \langle K_n, Q_n \rangle$, $n \in \mathbb{N}$.

Number of intakes $N(t) = \sum_{n \in \mathbb{N}} \mathbb{I}\{T_n \leq t\}$

The process X is piecewise-deterministic with càd-làg trajectories such that

$$X(t) = X(0) + B(t) - \sum_{n=1}^{N(t)+1} \int_{T_{n-1}}^{T_n \wedge t} r(X(s), \theta_n) ds, \qquad (2.2)$$

Markovian structure of the accumulative process

Time necessary for the ingested contaminant (without further intake) to decrease from $x_0 > 0$ to $x \in (0, x_0)$ given by

$$\tau_\theta(x_0, x) = \int_x^{x_0} \frac{1}{r(y, \theta)} dy.$$

Condition ($\mathcal{C}_1$): $H(\{\tau_\theta(x_0, 0) < \infty\}) = 1$ for some $x_0 > 0$

Put $\theta(t) = \sum_{n \in \mathbb{N}} \theta_n \mathbb{I}_{\{t \in [T_n, T_{n+1}[\}}$: record of the metabolic parameter and $A(t) = t - T_{N(t)}$ the backward recurrence time then $(X(t), \theta(t), A(t))_{t \geq 0}$ is strongly Markov.

Tools to study the embedded process : Harris recurrence, Meyn and Tweedie (1996),Embrechts, Kluppelberg and Mikosch (1997), ruin models. Assmussen (2000)(2003), Assmussen and Albrecher (2010), ruin models, queuing or storage system models.

A particular example :KDEM, exponential decrease with fixed θ

The pharmacokinetic exponential model

$$r(x,\theta) = \theta x. \tag{2.3}$$

Bertail, Clémençon and Tressou (2008),(2011)
The embedded chain (the process at times T_n) $\tilde{X}$ satisfies the following autoregressive equation with random coefficients

$$X_{n+1} = e^{-\theta_n \Delta T_{n+1}} X_n + U_{n+1}, \text{ for all } n \geq 1, \tag{2.4}$$

and has transition probability $\Pi(x, dy) = \pi(x, y)dy$ with transition density

$$\pi(x,y) = \int_{\theta \in \Theta} \int_{t=\frac{1}{\theta} log(1 \vee \frac{x}{y})}^{\infty} f_U(y - xe^{-\theta t}) G(dt) H(d\theta), \tag{2.5}$$

See also P. Bougerol et N. Picard (1992).
This can also be seen as a shot noise model.-> Calculation of the ruin probability (cf McCormick(1989)), of the extremal index when contamination is heavy tailed.

Theorem

Assume that

- *(H1)* $\mathbb{E}[log(1 \vee U_1)] < \infty$.

Then $\tilde{X}$ *is recurrent positive with stationary probability distribution* $\tilde{\mu}$.
If one assume further that:

- *(H2) there exists some* $\gamma \geq 1$ *such that* $\mathbb{E}(U_1^\gamma) < \infty$,

then $\tilde{X}$ *is geometrically ergodic,* $\tilde{\mu}$ *has finite expectation and there exist constants* $R < \infty$ *and* $r > 1$ *such that, for all* $n \geq 1$, $x > 0$,

$$sup_{\{\psi, |\psi(z)| \leq 1+z^\gamma\}} \left| \int_{y=0}^{\infty} \psi(y) \Pi^n(x, dy) - \tilde{\mu}(\psi) \right| \leq R(1+x^\gamma) r^{-n}, \tag{2.6}$$

denoting by Π^n *the* n*-th iterate of* Π *and with* $\tilde{\mu}(\psi) = \int_{y=0}^{\infty} \psi(y) \tilde{\mu}(dy)$ *for any* $\tilde{\mu}$*-integrable function* ψ.

Theorem

Suppose finally that

- *(H3) The r.v. U_1 is regularly varying with index $\alpha > 0$.*

Then the stationary law $\tilde{\mu}$ has regularly varying tail with index α. The ruin probability is regularly varying with index α.

Remark : small tail (exponential tails) implies small tails of the stationary distribution and of the ruin probability. Power tail of the intakes (regularly varying with index α = Pareto like) implies power tail for the stationary distribution and the ruin probability. Not completely realistic for food risk assessment especially with contaminant with a very long half life (ex: Methyl-mercury).

Remark : for fat tail the limiting behavior, the ruin probability on an infinite horizon does not depend on the elimination process. Ruins occurs for a big intake. True even for the random release KDEM and other elimination form. Not realistic...

Introducing dependence between the intakes

joint works with Charles Tillier (2019).

- Introduce simple $AR(p)$ structure motivated by previous modelisation of consumption/intakes
- Conditions of stability and existence of a stationary distribution : check the condition of Kluppelberg and Pergamentchikov (2007), Extremal behavior of models with multivariate random recurrence representation.
- Does not change much... Explicit formula more involved but the limiting behavior of the process is quite similar. Except that we have clusters of maximums due to the dependance structure. See Bertail, Clémencon and Tillier (2015)(2019), EJS for proposal to estimate the extremal index in this framework.

A more realistic model for the assimilation/pharmacokinetic elimination process

Problem :

- How can we take into account the assimilation process?
- A large quantity is "almost directly" assimilated or eliminated by parts of the organism, assimilation slow down the elimination process.
- Behavior linked to compartimental models, intake are transferred from to other parts of the organism (blood, liver, brain etc.)

A shot noise model for the assimilation/pharmacokinetic elimination process

Minor modifications of some work in hydrology : M. Lefebvre et J.L. Guilbault (2008). Using filtered Poisson processes to model a river flow, Applied Mathematical Modelling, 32 , 2792-2805.

$$X(t) = \sum_{n=1}^{N(t)} R(t, T_n, U_n).$$

with

$$R(t, T_n, U_n) = a^{-1} U_n (t - T_n)^k e^{-\theta(t - T_n)}$$

and $a = a(\theta, \tau) = (k/\theta)^k exp(-k + \theta\tau)$.
Main advantage : easy to estimate parameters by computing moments (moments estimators) Drawbacks : too smooth for intakes, we loose the nice Markov structure.

We rather consider the "Markovian" discrete structure with additional parameters

$$X(T_n) = a^{-1}(T_n - T_{n-1} + \tau)^k exp(-\theta(T_n - T_n))X(T_{n-1}) + \lambda W_n$$

for $0 \leq \tau < k/\theta$ and $a = a(\theta, \tau) = (k/\theta)^k exp(-k + \theta\tau)$ or a an amplification factor to be estimated. $\lambda \in]0, 1[$ plays on part of the contaminants directly absorbed.
and for $t \in [T_{n-1}, T_n]$

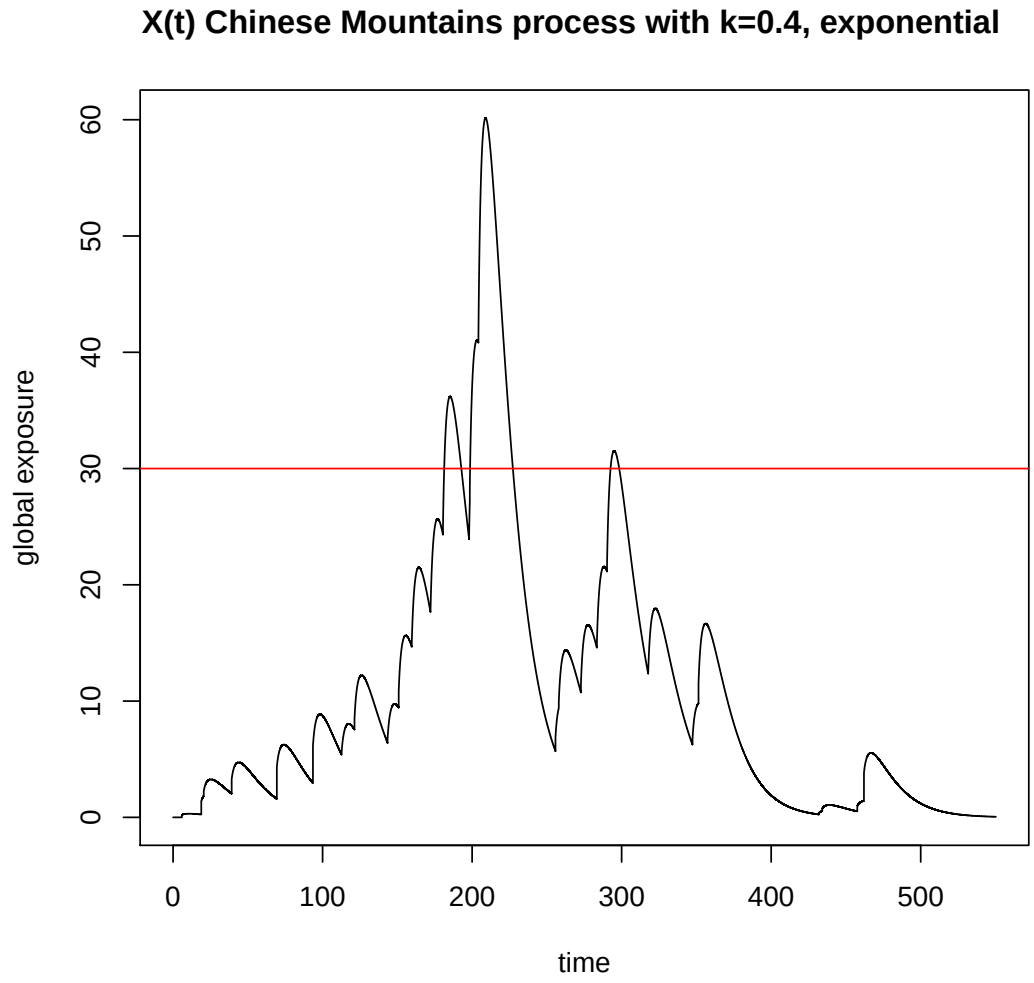
$$X(t) = a^{-1}(t - T_{n-1} + \tau)^k exp(-\theta(t - T_{n-1}))X(T_{n-1}^+)$$

that is corresponding to the elimination pharmacokinetic between intakes driven by

$$dx(t)/x(t) = k/(t + \tau) - \theta$$

Does not satisfy the conditions of B., Clémençon and Tressou(2008)(2012).

If k and τ are too large then the contaminant is never eliminated and we loose recurrence. If $k = 0$ and $\tau = 0 = 1$ we recover the original KDEM model.



What is the impact of the assimilation delay on the long term behavior of the process? Huge!

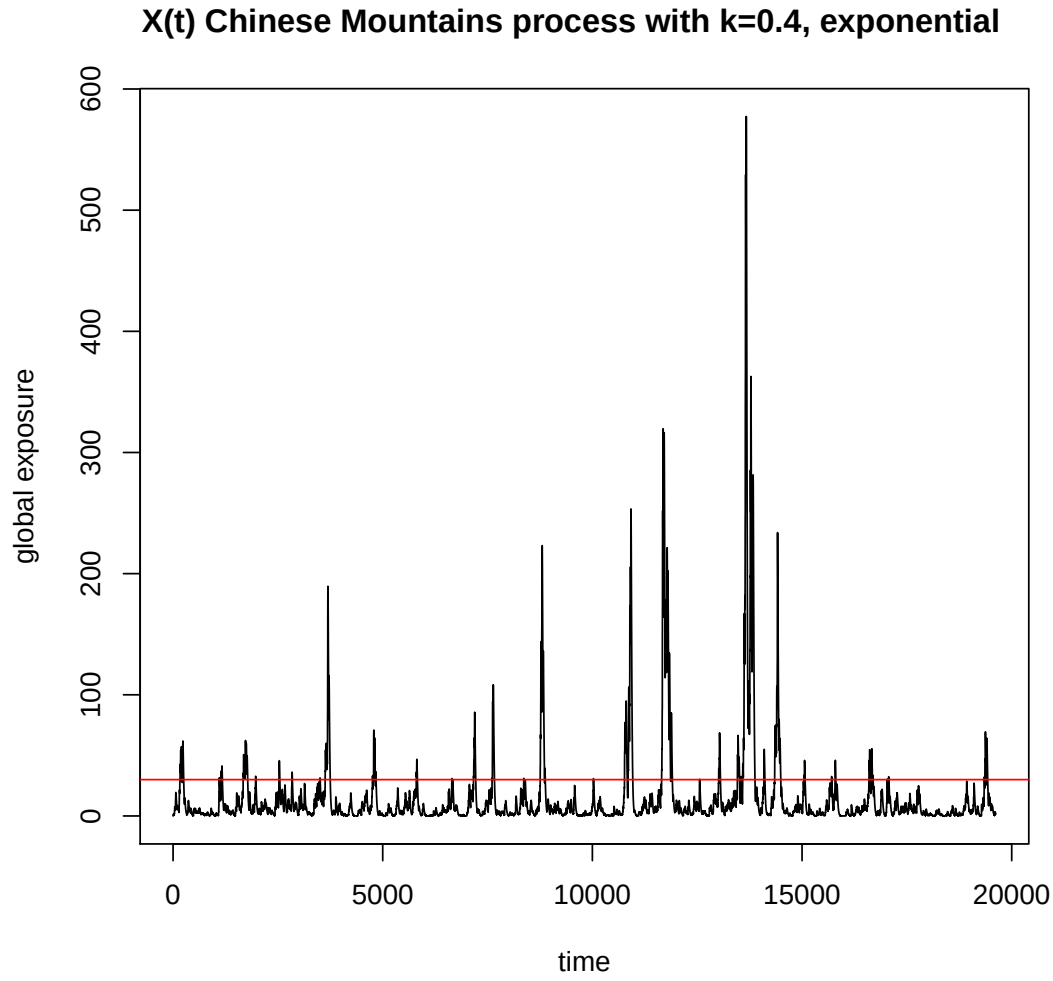


Figure: A simulated path with $\tau = 1$ and $k = 0.4$ and $T = 3.5 years$, exponential intakes, exponential inter-arrivals

Conditions of irreducibility and recurrence

This process falls into the framework of Kesten(1973)(1974), see also Kluppelberg and Pergamentchikov (2007), D. Buraczewski, E. Damek, T. Mikosch, and J. Zienkiewicz (2013)

Kesten, H. (1973). Random difference equations and renewal theory for products of random matrices. Acta Math. 131 207Ű248. Kesten, H. (1974). Renewal theory for functionals of a Markov Chain with general state space, Annals of probability, 2, 355-386.

The solution of the stochastic recurrence equation has a marginal distribution with power law tails, while the noise sequence of the equations can have light tails.

Theorem

Assume that

- ΔT_n *has light tail : for* $c > 0$, $Eexp(c\Delta T_n) < \infty$
- $k > 0$ *and* $\tau \geq 1$, *such that for some* $\epsilon > 0$

$$E(a^{-\epsilon}(\Delta T_n + \tau)^{\epsilon k} exp(-\theta \epsilon \Delta T_n)) < 1$$

- *there exists* α_0 *such that*

$$E(a^{-\alpha_0}(\Delta T_n + \tau)^{\alpha_0 k} exp(-\theta \alpha_0 \Delta T_n) > 1$$

, while

$$E(|U|_0^{\alpha}) < \infty$$

Then (Kesten(1973)), there exists $\alpha \in [0, \alpha_0]$, *such that*

$$E(a^{-k}\Delta T_n + \tau)^{\alpha k} exp(-\theta k \Delta T_n) = 1$$

and the stationary distribution of the embedded chain is regularly varying with index α.

Compartments models with assimilation and releases

Several compartments in the body :

- Stomach $X_1(t)$
- Liver $X_2(t)$
- Intestine (colon)
- Pancreas
- ...
- Belly, Breast (fat stocks)
- Brain $X_k(t)$

Compartments models aim at understanding the dynamical accumulation process between these parts of the body. Moriarty (1984), Persistent Contaminants, Compartmental Models and Concentration along Food-Chains. Ecological Bulletin. van Hattum,B.et al. (1989). Environ. Pollut. 62, 129Ű151. See references in the study on Cd and Hg by Gestin et al. (2021). One and multi-compartments toxico-kinetic modeling to understand metalsŠ organotropism and fate in Gammarus fossarum, Environment International.

More realistic modeling of the deterministic behavior between intakes, with compartments models

A model without assimilation process is proposed in Gestin et al. (2021)

For $t \in [T_n, T_{n+1}]$

$$dX_1(t) = k_1/(t+\tau_1)X_1(t) - \theta_{1,1}X_1(t) + \sum_{i=2,\ldots,K} \theta_{1,i}X_i(t)$$

and for $j = 2$ to K

$$dX_j(t) = k_j/(t+\tau_j)X_1(t) - \theta_{j,j}X_1(t) + \sum_{i=1,.,j-1,j+1..,K} \theta_{j,i}X_i(t)$$

Very easy to simulate the process (multivariate non linear AR models with random coefficients), if we know the toxico-cinetic parameters k_j, τ_j (for instance for $K = 3$, for Cd, Hg) and the matrix $\theta_{j,i}$, to evaluate the probability/time to be over a threshold when the risk is high. On going works for small risks (use of multi-level splitting techniques, Glasserman(1996), Cérou-Guyader(2007)).

Conclusions

- Need for more realistic model which takes into account the assimilation process, the compartments in the body.
- Small tails of intakes can yields large tail probability for the accumulated process in these models: more appropiate to the data at hand.
- Process easy to simulate for each individual, eventually using rare event simulations (multi-level splitting) : see BCT(2010) and ongoing works for an application to methyl-mercury.
- TO DO : Theoretical study/ estimation of the parameters for multidimentional compartments models.

Conclusions

- At the moment no data available to estimate precisely the $\theta_{j,i}$ for most contaminants/nutrients
- data limited to a few compartments (3 for Hg, Cd)
- Current attempt to apply this method individually by just collecting every day consumption of a few individuals and transform into nutrient/ contamination exposure.
- At a larger scale, can point out the products which may be at risk and which parts of the body are more affected according to contaminants
- Estimate the impact on contaminents of following nutriscore or not/ implementing fat tax or not etc...

Thank you for your attention.