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Size rules life, but does it in the assessment of medical vigilance best practice? Towards a testable hypothesis

Laurent Seuront[a,*], Dorine Seuront-Scheffbuch[b]

[a] CNRS, Univ. Lille, Univ. Littoral Côte d'Opale, UMR 8187, LOG, Laboratoire d'Océanologie et de Géosciences, F 62930 Wimereux, France
[b] Agence Régionale de Santé (ARS) de Picardie, 52 rue Daire, CS 73706, 80037 Amiens Cedex 1, France

HIGHLIGHTS

- We infer the applicability of scaling concepts to haemovigilance.
- Haemovigilance is based on the occurrence of serious adverse reactions and events (SARE) following blood transfusion (BT).
- SARE is essentially a power-law function of BT.
- We show the existence of two power-laws depending on BT.
- Beyond a critical threshold of BT, the safety of the transfusion process is increased.

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ABSTRACT

The goal of this paper is to infer the applicability of scaling concepts to haemovigilance based on the study of the relationship between severe adverse reactions and events (SARE) and blood transfusions (BT). We hypothesize that in a haemovigilance operating optimally, SARE should be a power-law function of BT as SARE $= \alpha BT^{\beta}$. We investigated the relationship between yearly BT and the related SARE reported in 12 French hospitals of the Picardie State from 2004 to 2015. First we found that when integrated over the whole period 2004–2015, SARE were significantly described by a power-law function SARE $\propto$ BT$^{1.51}$ for 10 of the 12 hospitals considered. The numbers of SARE in these two hospitals is drastically over-estimated by this power-law, that is 1.9- to 4.3-fold lower than those predicted by the power-law. When considered on a yearly basis, we consistently found that SARE was also significantly described by a power-law function of the form SARE $\propto$ BT$^{1.44}$ for 10 of the 12 hospitals considered. In turn, the occurrence of SARE in the two other hospitals was strongly over-estimated by this power-law, though it is also significantly described by another power-law, SARE $\propto$ BT$^{1.11}$. We specified these results through separate yearly analyses and found the relationship between SARE and BT was best described by a power-law with $\beta = 0.90$ in 2004, a linear relationship from 2005 to 2007 and a power-law with β ranging from 1.49 and 1.92 from 2008 to 2014. Finally, in 2015, the relationship between SARE and BT was significantly described by a power-law SARE $\propto$ BT$^{1.17}$ for the 12 hospitals considered. Overall, our results suggest that hospitals performing more blood transfusions are more efficient as the observed negative effects of blood transfusions increase relatively slower than in hospitals performing less transfusions.

* Corresponding author.
E-mail address: laurent.seuront@cnrs.fr (L. Seuront).

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1. Introduction

Over the last decades, it has become increasingly and mesmerizingly evident that the growth of the multiple networks that sustain life, from intracellular to cardio-vascular patterns, but also from anthills and beehives, to cities, economies and companies can be expressed as simple '*universal mathematical laws*', fundamentally stating that doubling in size requires only 80–85% increase in infrastructure and energy consumption [1–3]. These laws find their roots in the early work of Otto Snell in 1892 on the allometric dependence of brain weight on body weight and mental abilities [4]. The term allometry was later formalized [5,6] as a conventional designation in biology of the phenomena of differential growth of organs, tissues and activity.

One of the most fundamental allometric scaling laws, introduced by Max Kleiber in 1932, relates how basal metabolic rate r of endothermic vertebrates (birds and mammals) changes with body mass M as $r \propto M^{3/4}$ [7]. A striking consequence of Kleiber's law is that a horse may be 10,000 times heavier than a mouse, it only consumes 1000 times more energy (*i.e.* $10{,}000^{3/4} = 1000$). It is then more efficient to be larger as smaller animals are less energy efficient. Noticeably the same phenomenon holds from the cellular to the population level. More generally, there is now compelling evidence that despite spanning more than 21 orders of magnitude in size from microbes to whales, living organisms obey a host of remarkably simple and systematic empirical scaling laws that dictate how biological quantities such as metabolic rate, time scales (*e.g.* cardiac dynamics and locomotion), and weights and shapes of component parts change with size [8–11]. The mesmerizing universality of these laws is telling us something essential about the way life is organized and the constraints under which it has evolved.

More fundamentally, the existence of a power-law between two quantities is the results of the interplay between a range of internal and external conflicting forces that converge towards an optimization of performance. For instance, one of the first models accounting for the scaling variant behavior in cardiac dynamics, demonstrates that competing/conflicting inputs of the sympathetic (increasing heart rate) and parasympathetic (decreasing heart rate) systems with non-linear feedback are key to emerging dynamics characterized by power-laws [12]. This is the reason why both mammal and plant vascular systems obey the same scaling law [1] as they both fulfill the same function, *i.e.* transporting a fluid in a ramified network against gravity. Scaling laws can, however, exhibit lower and upper limits. For instance, Newton's Universal Law of Gravitation put an upper limit to the size of animals, which is fundamentally restricted by both the mechanical strength of bone and the mass of the Earth [9,13]. In other words, an elephant could not fly and a whale could not walk even if they respectively had wings and legs. Similarly, the smallest size of capillary vessel is dictated by both the size of the single layer of rolled-up endothelial cells forming the vessel and the size of the maximally deforming erythrocyte to pass though. Scaling laws also appear to obey another principle called symmorphosis, or economy of design [14]. This principle lies on the idea that biological structures and functions are designed so as to meet but not exceed the maximal demand. As a consequence, the design which confers the highest fitness provides for the maximum demand [15]. This principle further implies that any significant deviation of an individual or species from the value predicted from a scaling law indicates a sub-optimal and often pathological design, which implies a substantial fitness cost (*e.g.* acromegalic gigantism and excessive obesity), or a special adaptive response to selective pressures not operating on the other organisms or individuals used to derive the equation [16,17]. A typical example of these transitions is provided by the dependence of the exponents which define power-laws in physiologic dynamics (sleep stage and arousal transitions) to metabolic rate and body mass; see [18], their Fig. 4. The principles discussed above apply to a range of complex systems (*e.g.* medicine, individual and collective behaviors, species diversity, evolution, palaeontology, economics, sociology, linguistics, sports, and various areas of physics and chemistry) where fitness or more generally some performance criterion is optimized. For instance, proxies of city energy usage, such as number of gas stations and length of electric cables, scale sub-linearly with the size of a city, indicating that people living in bigger cities are more energy-efficient. As such scaling laws have been suggested as a design principle, as a scaling design is structurally and functionally efficient as it requires little energy to sustain itself [2,19–21]. More specifically, a remarkable review [22] poses the fundamental question: "*Do biological phenomena obey underlying universal laws of life that can be mathematized so that biology can be formulated as a predictive, quantitative science?*" and further offers scaling as an exemplar of such universal behavior in biological sciences. In that regards, it is remarkable that in the context of human physiology, diverse organ systems that operate over various ranges of time scales (e.g. heart rate fluctuations, respiratory inter-breath intervals, gait dynamics, wrist motion, brain dynamics of arousals during sleep) all exhibit scaling laws with similar exponents that are close to unity [23–28].

However, despite the plethora of medical literature showing modification and loss of scaling properties under various clinical conditions (*i.e.* stress, age, parasitism, disease; [29,30]), so far no attempt has been made to apply scaling concepts in the context of medical vigilance, *i.e.* the set of organized surveillance procedures related to adverse or unexpected reactions in patients following a medical procedure, and devoted to prevent their occurrence and recurrence. By analogy with the various systems discussed above where the interplay between various (internal and external) forces leads to power-laws, the number of reported adverse transfusion events is impacted by different, and potentially conflicting, forces. First, the resources (both funding and staff) allocated to hospitals to prevent such events (i.e. to reduce what would be the natural frequency of adverse events if those precautions were not in place), hence the effectiveness of the medical vigilance varies between hospitals. Second, it is well established that many adverse events are either un-noticed, un-recognized, or un-reported, which further perturbs the observed occurrence rate. The identification of a power-law signature in a vigilance process may, however, be considered as a sign of robustness by analogy with the power-law behaviors exhibited by a range