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Dimensional analysis shows that mice models could lead to drug over dosages in humans

Research Article

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Summary

In this short paper the scaling of the metabolic rate is used to predict the optimal specific drug dosage, suggesting that the usually adopted physical units (i.e. mg/Kg or drops/Kg) are not the best choice, naturally leading to over dosages when increasing the size-scale. Our argument justifies and improves empirical approaches and could represent a powerful shortcut for experimentally optimizing the drug dosage, e.g. from mice models to humans in the cancer therapy.

I. Introduction

Allometric laws have been known for more than 70 years, see (West et al, 1997) and related references, and have been used for some time in pharmacological studies and to model drug clearance (e.g., see (Boxenbaum, 1980, 1982; Mahmood and Balian, 1996, 1999; Khor et al, 2000; Tang et al, 2005; Lowe et al, 2007) and the book (Mahmood, 2005). Allometric scaling has also been used very recently in tumour growth (Castorina et al, 2006; Delsanto et al, 2008a,b; Guiot et al, 2006a,b; 2008). In spite of this, the physical units used for specific drug dosages are often mg/Kg or drops/Kg (Boxenbaum, 1980, 1982; Mahmood and Balian, 1996, 1999; Khor et al, 2000; Tang et al, 2005; Lowe et al, 2007), which are substantially incompatible, as we are going to demonstrate, with such anomalous scalings. In contrast, a simple dimensional analysis is here invoked to justify and improve classically empirical approaches (see (Boxenbaum, 1980, 1982; Mahmood and Balian, 1996, 1999; Khor et al, 2000; Tang et al, 2005; Lowe et al, 2007)), providing a powerful shortcut for experimentally optimizing the drug dosage, e.g. from mice models to humans in the cancer therapy.

II. Size-effects on specific drug dosages

The simplest approach to derive a preliminary estimation of the drug dosage $m(M)$ needed by organisms of different masses M is to assume as a constant the specific drug dosage $m(M)/M$. This argument is today often invoked within different species and inside the same species too (Boxenbaum, 1980, 1982; Mahmood and Balian, 1996, 1999; Khor et al, 2000; Tang et al, 2005; Lowe et al, 2007), naturally leading to the use of mg/Kg or drops/Kg for the physical units of the specific dosage.

These physical units are implicitly based on the assumption that the metabolic rate is proportional to the mass. In spite of this, the metabolic rate is proportional to the mass raised to an exponent p close to 3/4 (West et al, 1997) and in general comprised between 2/3 and, at least theoretically, 1 (see the box in (Carpinteri and Pugno, 2005); this is the analog (Pugno, 2007b) of what happens for the energy dissipated in solids, that is proportional to the volume of the solid raised to an exponent ranging between 2/3 (energy dissipated over a surface, brittle materials) and 1 (energy dissipated in the volume, ductile materials; see (Carpinteri and Pugno, 2005) and related references). However, the situation in living organisms is different, with metabolic laws involving a power p close to 2/3 in small animals, for which diffusion is the main mechanism of nutrient delivery to cells, and about 3/4 in bigger animals (where the nutrient distribution system has fractal features, according to (West et al, 1997)). Hypothesizing that drugs arrive at the pertinent cells following the same path as the nutrients, p could be roughly between 2/3 and 3/4.

Thus, as the energy density is size-dependent, leading to the well-known "smaller is stronger" size-effect in structural and material mechanics, also the specific dosage must be size-dependent. Accordingly, not mg/Kg but mg/Kg^p should be the true physical unit to build a mass-independent (optimal and "fractal") specific dosage χ. Or, in other words, m/M is expected to be mass-dependent, in the form of:

$$\frac{m}{M} = \chi M^{p-1} \qquad (1)$$

According to Eq. (1), the specific drug dosage is mass-dependent and cannot be considered, as usually assumed, to be a constant. In particular, since $p<1$, the larger the mass the smaller the specific dosage. The implications are remarkable. For example, in drugs for both children and adults, where a number of drops per Kg is suggested (see commercially available drugs), we expect over dosages for adults or lower dosages for children. For example, considering $p=3/4$ and $M_{man}/M_{child}=10$, Eq. (1) would predict that $(m/M)_{man}/(m/M)_{child}\approx 0.56$. Similarly, in different species, over dosages are expected in larger animals, e.g. in humans when the specific dosage is directly derived from mice models. For example, considering $p=3/4$ and $M_{man}/M_{mouse}=1000$, Eq. (1) would predict that $(m/M)_{man}/(m/M)_{mouse}\approx 0.18$. Even if the Food and Drug Administration (FDA) would not approve or suggest drug dosages for humans based only on mice experiments, the use of Eq. (1) would represent a powerful shortcut for experimentally optimizing the drug dosage. Eq. (1) presents only two free parameters, χ and p, which can thus straightforwardly experimentally derived by a classical linear fit in a bilogarithmic plane. The validity of the scaling (1) proportional to $M^{2/3-1}$ and predicted by our dimensional analysis is fully confirmed by experiments (see (Boxenbaum, 1980, 1982; Mahmood and Balian, 1996, 1999; Khor et al, 2000; Tang et al, 2005; Lowe et al, 2007), showing that the optimal dosage is expected between different species as proportional to $M^{0.7\text{-}0.8}$. Thus, probably, a similar scaling could be applied within the same species.

More precise predictions would have to take into account the observed weak variability of p, from 2/3 towards 1 by increasing the mass M (Carpinteri and Pugno, 2005; Guiot et al, 2006). Thus, in analogy with solid state physics (Carpinteri and Pugno, 2005), we propose the use of the following asymptotic matching:

$$\frac{m}{M} = \left(\frac{m}{M}\right)_{macro} \sqrt[3]{1+\frac{m_{micro}}{M}} \qquad (2)$$

Eq. (2) has two characteristic constants: $(m/M)_{macro}$, that is the value of the optimal dosage at (infinitely) large size-scale, and m_{micro}, that is a characteristic biological mass governing the transition from micro to macro. Having also Eq. (2) only two free parameters its best-fitting is trivial.

A third and last law is proposed by removing the singularity in Eq. (2), describing that at vanishing size-scale the drug dosage mathematically tends to infinity (following the procedure suggested in (Pugno, 2007a)):

$$\frac{m}{M} = \left(\frac{m}{M}\right)_{macro} \sqrt[3]{1+\frac{m_{micro}}{M+q}} \qquad (3)$$

where the additional parameter q is defined noting that

$$\left(\frac{m}{M}\right)_{nano} = \left(\frac{m}{M}\right)_{macro} \sqrt[3]{1+\frac{m_{micro}}{q}}$$

must represent the specific dosage for vanishing size-scale (nanoscale). Eq. (3) is evidently more general than Eq. (2) but its best-fitting is less trivial, since it involves three free parameters.

III. Conclusions

Concluding, we want to stress that the classical simplest assumption, i.e. basically considering Eq. (1) with $p=1$, Eq. (2) with $m_{micro}=0$ or Eq. (3) with $m_{micro}=q=0$, is not the best choice to experimentally optimize drug dosage; in contrast, Eqs. (1-3) are direct consequences of the anomalous universal scaling of the metabolic rate and are thus expected to have a general character.

The use of Eqs. (1-3) could lead to a powerful shortcut to reach the optimal drug dosage.

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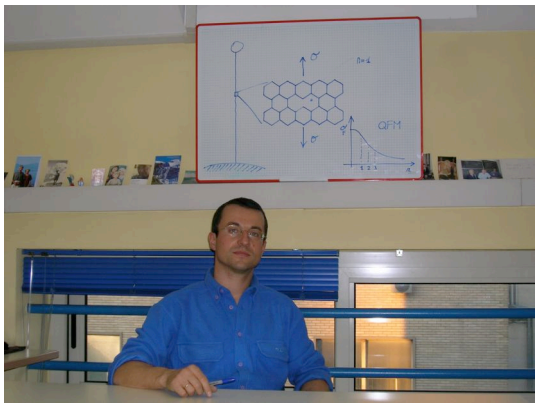

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