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Going to extremes: the Goldilocks/Lagom principle and data distribution

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3 1 Going to extremes: the Goldilocks/Lagom principle and data distribution
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5 2 Henry J Leese ^{1*}, Thozhukat Sathyapalan ^{2,3}, Victoria Allgar ⁴, Daniel R Brison ^{5,6} & Roger G
6 3 Sturmeay ¹
7 4

8 5 1, Centre for Atherothrombosis and Metabolism, Hull York Medical School, University of Hull,
9 6 Hull, HU6 7RX, UK

10 7 2, Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University
11 8 of Hull, Hull, HU6 7RK UK

12 9 3, Department of Endocrinology, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK

13 10 4, Hull York Medical School, University of York, York YO10 5DD, UK

14 11 5, Maternal and Fetal Health Research Centre, Division of Developmental Biology and
15 12 Medicine, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of
16 13 Manchester, Manchester Academic Health Sciences Centre, St. Mary's Hospital,
17 14 Manchester, M13 9WL, United Kingdom

18 15 6, Department of Reproductive Medicine, St. Mary's Hospital, Manchester University NHS
19 16 Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, M13 9WL,
20 17 United Kingdom

21 18 * To whom correspondence should be addressed: henry.leese@hyms.ac.uk
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32 32 **Abstract**

33 23 Numerical data in biology and medicine are commonly presented as mean or median with
34 24 error or confidence limits, to the exclusion of individual values. Analysis of our own and
35 25 others' data indicates that this practice risks excluding 'Goldilocks' effects in which a
36 26 biological variable has a range of expression between 'too much' and 'too little' with a region
37 27 in between where its function is 'just right', or as termed in Sweden, 'Lagom', which
38 28 symbolises 'moderation' and 'in balance. This was confirmed by a narrative search of the
39 29 literature using the PubMed Database, which revealed numerous relationships of biological
40 30 and clinical phenomena of the Goldilocks/Lagom form including quantitative and qualitative
41 31 examples from the health and social sciences. Some possible mechanisms underlying these
42 32 phenomena are considered. We conclude that retrospective analysis of existing data will
43 33 most likely reveal a vast number of such distributions to the benefit of medical understanding
44 34 and clinical care and that a transparent approach of presenting each value within a data set
45 35 individually should be adopted to ensure a more complete evaluation of research studies in
46 36 future.

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48 38 **174 words**
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53 41 Going to extremes: the Goldilocks/Lagom principle and data distribution
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55 42 **Text**
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58 44 Introduction
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3 45 Numerical data in science and medicine have traditionally been presented as mean or
4 46 median values with standard errors or standard deviations. Such data commonly take the
5 47 form of tables, bar graphs or line graphs. However, as (1) point out, this practice poses a
6 48 problem since different distributions of data can lead to the same bar or line graph. This was
7 49 well illustrated recently by (2) who used illustrative data from a hypothetical experiment to
8 50 examine the impact of three different cell lines on drug receptor activation and showed that a
9 51 variety of distributions of individual data points can lead to similar bar graphs with the same
10 52 mean (Fig 1).

11 53 The attention paid to individual variation in cellular and molecular biological and clinical
12 54 studies is relatively recent, but has been well-known for many years to ecologists, especially
13 55 following the publication by Albert F. Bennett, in 1987, of an influential article entitled: *Inter-*
14 56 *individual variability: an underutilized resource*. Bennett, an ecological physiologist, pointed
15 57 out that mean values with confidence intervals about the mean, once published tend to ‘--
16 58 *take on a life of their own, and become the only point of analysis and comparison*’ to the
17 59 exclusion of the individual values, and their potential significance. Bennett referred to this
18 60 tendency as ‘*the tyranny of the Golden Mean*’, and as an alternative, advocated the analysis
19 61 of inter-individual variability, i.e., the full range of individual values, he considered could
20 62 provide the observer with a greater interpretative repertoire.

21 63 In the time since Bennett’s paper, there has been a movement away from the tyranny of the
22 64 mean in many areas of biology, notably in ecology (3). Examples are provided by Stephen J
23 65 Gould (4), who wrote an article on ‘*The median isn’t the message*’, Hayes and Jenkins (5) on
24 66 individual variation in mammals, and Lloyd-Smith (6) on the spread of epidemics of human
25 67 disease.

26 68
27 69 Our interest in inter-individual variability arose particularly from research in which we have
28 70 been involved on (a) the development and metabolism of single preimplantation mammalian
29 71 embryos (DB, HL, RS) and (b) of glycaemic control in individual human subjects (TS).

30 72 (a) Development and metabolism of single preimplantation embryos

31 73 Data which illustrate the value of distributions rather than mean or median values were
32 74 provided by (7) who measured the consumption of the essential nutrient, pyruvate, by single
33 75 bovine preimplantation embryos at the zygote stage (1-cell fertilised egg; day 1 of
34 76 development). The experiments revealed considerable heterogeneity between individual
35 77 embryos such that it was possible to divide them prospectively into 3 groups - of ‘high’,
36 78 ‘intermediate’ and ‘low’ pyruvate consumption at an early stage (day 2) - and track their
37 79 subsequent development to the blastocyst stage, a critical developmental endpoint. These

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3 80 data indicated that intermediate values of pyruvate consumption correlated with viability
4 81 (capacity to form a blastocyst), though with considerable overlap between the categories.
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6 82 Put another way, which takes account of this overlap, plotting individual values revealed the
7
8 83 existence of an optimal 'range' of metabolic activity. This concept was developed in a follow-
9
10 84 up paper (8) in which we proposed that the optimal range was equivalent to a 'Goldilocks
11 85 zone' or as it is known in Sweden, of 'lagom', meaning 'just the right amount', in which
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13 86 embryos with maximum developmental potential are located (see a*).

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16 88 (b) Glycaemic control

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19 90 Plasma Haemoglobin A_{1c} (HbA_{1c}) is the standard measure of glucose control and is
20 91 recommended for use as a diagnostic test for humans with diabetes mellitus (9). There is an
21 92 association between the extent of high blood glucose as measured by HbA_{1c} and the risk of
22 93 death and of macrovascular and microvascular disease in patients with type 2 diabetes
23 94 (T2DM) (10). In the landmark United Kingdom Prospective Diabetes Study, intensive
24 95 glycaemic control aiming for a lower HbA_{1c} of 7% was associated with improved outcome in
25 96 newly diagnosed patients with type 2 diabetes (T2DM) (11). This finding was then
26 97 extrapolated to all patients with T2DM, and as a result, low HbA_{1c} levels were
27 98 recommended for management of patients with T2DM. However, concerns arose as data
28 99 from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial began to emerge
29 100 showing increased all-cause mortality and cardiovascular mortality in the intensive treatment
30 101 group who were treated with antihyperglycaemic agents aiming for a lower HbA_{1c} target of
31 102 6% compared with conventional antihyperglycaemic treatment in patients with T2DM aiming
32 103 for HbA_{1c} of 7-7.9%. These results led to early termination of the trial (12). Further studies
33 104 have demonstrated that both high and low levels of HbA_{1c} are associated with an increased
34 105 risk of all-cause mortality suggesting a "Goldilocks' or 'lagom" state in between.

35 106

36 107 Similar "U" shaped associations with HbA_{1c} and all-cause mortality have also been shown
37 108 for type 1 diabetes (13). Even in patients without diabetes, extremes of glycaemia as
38 109 measured by HbA_{1c} are associated with adverse clinical outcomes including cardiovascular
39 110 events and all-cause mortality. Similar increases in mortality in either extremes are seen
40 111 with body weight, blood pressure, birth weight, cholesterol and other cardiovascular risk
41 112 factors.

42 113

43 114 Goldilocks and Lagom

44 115 The Goldilocks zone has been defined mathematically by (14) in the context of xenobiotic
45 116 ligand binding to nuclear receptors as a '*Non-monotonic receptor-mediated dose-response*

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3 117 *curve*' (NMDRC), and by (15) in the context of endocrine disrupting chemicals as 'a
4 118 *response where the slope of the curve changes sign from positive to negative or vice versa*
5 119 *somewhere along the range of doses examined*'. These are valuable definitions because
6 120 they can be applied to all non-linear distributions including U-shaped, inverted U-shaped, J-
7 121 shaped, sigmoidal and reverse sigmoidal.

11 122 The U-shaped curve is probably the most widely observed. It usually refers to the nonlinear
12 123 relationship between two variables, in particular, a dependent and an independent variable.
13 124 Because many analytical methods assume an underlying linear relationship, systematic
14 125 deviation from linearity can lead to bias in estimation of safe levels in exposure to nutrients,
15 126 drugs or toxic agents (for a discussion see section on *Mechanisms* below and (15)).
16 127

17 128 How widespread is the presence of a Goldilocks zone in biology and medicine?

18 129 We thought it might be instructive to discover how widely the notion of a 'Goldilocks zone' is
19 130 a feature of the wider biological literature, especially as applied to medicine. A
20 131 comprehensive search for information conducted on the *PubMed* database in early 2018
21 132 using the term 'Goldilocks' revealed 184 entries, all of which have been examined, together
22 133 with the grey literature. Only articles in English language were selected. A selection of 43 of
23 134 these publications has been presented (Appendix 1) as representative of the range of
24 135 phenomena which invoke the Goldilocks concept in order to increase biological and clinical
25 136 understanding. It should be emphasised that this is a narrative review rather than systematic
26 137 review and no judgement on the quality of these studies or of those which have been omitted
27 138 is implied. Patient/public involvement: No members of the public, nor patients were involved
28 139 in the synthesis of this manuscript.
29 140

30 141 Inspection of these examples reveals the wide range of biological and clinical phenomena in
31 142 which Goldilocks zones have been found including the health and social sciences which can
32 143 be qualitative rather than quantitative. It seems likely that a vast number remain to be
33 144 discovered and that authors could, in a relatively simple manner, derive added value from
34 145 their existing data by presenting distributions rather than median/mean values, and making
35 146 raw data available to the research community via online repositories. This would allow
36 147 systematic re-analysis by data scientists with an interest in the Goldilocks/Lagom concept.
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38 149 Mechanisms underlying the Goldilocks Principle and what is Lagom

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152 *Mechanisms which are global in scope*

153 We previously proposed an explanation that may account for Goldilocks/Lagom phenomena,
154 derived from our work on energy efficiency in early mammalian embryo development (8)
155 which made use of an account of general aspects of biological optimisation by (16). The
156 premise was that living things aim to function with the minimum input of energy, i.e., with
157 high energetic efficiency. To accomplish this will obviously require a threshold level of
158 metabolic activity to ensure a given process proceeds physiologically, while the upper limit
159 will be set by the capacity to increase metabolism vs '*the energy parsimony in almost*
160 *everything (living things) do*' (16). The Goldilocks/Lagom zone will obviously lie between
161 these extremes. The boundaries will be set by homeostatic mechanisms at all levels of
162 organisation. Such boundaries will be flexible in order to allow for the capacity to up- or
163 down-regulate metabolism in response to stress. Responses of these types have been
164 usefully categorised by ecologists to distinguish (a) modest changes in metabolism (up or
165 down within the *optimum* (Goldilocks/Lagom) range) from which the cell/organism can
166 recover (the so-called *Pejus* range) and (b) extreme perturbation beyond the optimum which
167 shifts metabolism irreversibly into a *Pessimum* range which is fatal (see Fig 2 in (17))

169 Some *specific mechanisms* for the production of non-monotonic receptor-mediated dose-
170 response curves (NMDRCs) were well summarised by (15) in terms of the effect of
171 endocrine disrupting chemicals, notably Bisphenol A on cells in culture, whole organisms,
172 laboratory animals and human populations. Interestingly, it was reported that NMDRCs were
173 common, comprising 20-30% of all studies examined, depending on the conditions; e.g., in
174 vivo vs in vitro. Mechanisms considered included cytotoxicity (18), inhibition of cell
175 proliferation (19); hormone receptors produced vs degraded (20); cell and tissue specific co-
176 factors (21) and pharmacological effects. At the whole body level, examples of NMDRCs in
177 nutrition are widespread, reflecting minimum requirements at the lower end of the distribution
178 and toxicity at the higher, for example, vitamin A. Vandenberg (15) concludes that '*strong*
179 *evidence for Non-monotonic receptor-mediated dose-response curves*' - - *question the*
180 *current risk assessment practice where 'safe' levels are predicted from high dose exposures*'

183 *Conclusion*

185 There has long been a fixation in the biological and clinical research communities with
186 presenting data solely as measures of dispersion (means and medians) and of central
187 tendency (e.g., standard deviation and interquartile range). We believe that the retrospective

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3 188 analysis of existing data could reveal numerous potential relationships with a
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5 189 Goldilocks/Lagom pattern.

6 190 Interestingly, the editors of the British Journal of Pharmacology ' (2) '*will now require that,*
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8 191 *where possible, numerical data (whether categorical or continuous), particularly involving*
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10 192 *two sets or paired data, should be presented using scatter-plots, before-after graphs, and*
11 193 *other forms in which each individual 'n' value is individually plotted, rather than using bar*
12 194 *charts. Authors presenting data as bar charts should state that a scatter plot or before–after*
13 195 *charts did not reveal unusual or interesting aspects of the data not obvious from the bar*
14 196 *chart'*.

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19 198 We believe the Journal should be complimented on this approach and urge all such journals
20 199 to adopt it.

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24 201 Author contributions:

25 202 H J Leese; conceived the study, conducted literature searches and wrote the first draft. All
26 203 authors then commented on subsequent drafts. V Allgar; provided statistical advice, DR
27 204 Brison; contributed to the initial concept and provided new material, as did RG Sturmey who
28 205 also prepared the manuscript for submission T Sathyalapan; contributed to initial concept;
29 206 provided new material and clinical expertise

30 207

31
32 208 Competing Interests:

33
34 209 The authors have no competing interests to declare in relation to this work.

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3 295 Fig 1; An illustrative example of a comparison of cell lines is described in Figure 1, which
4 296 shows that bar charts do not give the reader adequate information on the variability and
5 297 distribution of each sampled 'n'. This is because bar charts frequently do not adequately
6 298 convey major features of the dataset. As explained below, Figure 1 illustrates why moving
7 299 away from using bar charts to visualize the entire dataset is a necessary refinement that can
8 300 increase the transparency and reporting of data.

13 301 “ The extent of activation of a receptor in three cell lines a, b and c under baseline
14 302 (drug-naïve) conditions and following the addition of a drug is given in arbitrary units. The
15 303 same data sets are presented in three different ways: (A) bar chart, (B) grouped column
16 304 scatter plot with means and error and (C) before–after scatter plot. $n = 10$ (i.e. biological
17 305 replicates and not technical replicates). In this example, error bars represent the SEM
18 306 although authors should consider the sampling size and distribution of 'n' when choosing the
19 307 most appropriate way of showing experimental error [e.g. SD or confidence interval]”.

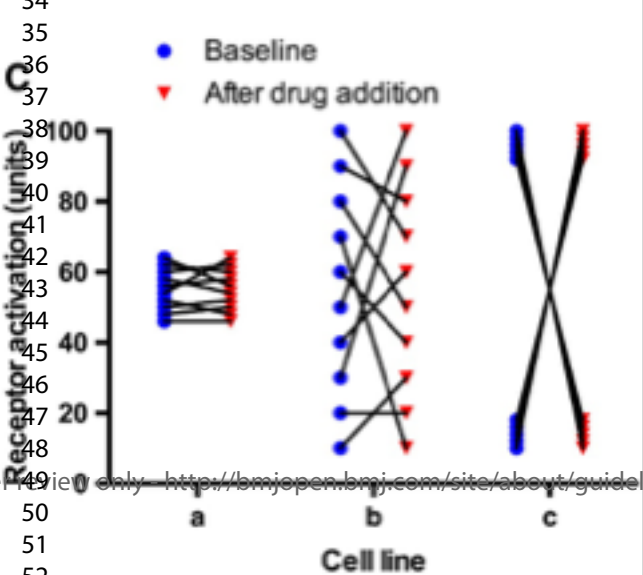
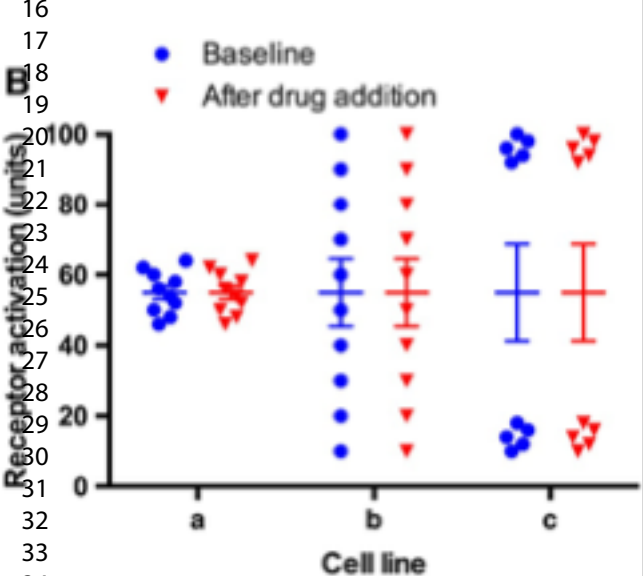
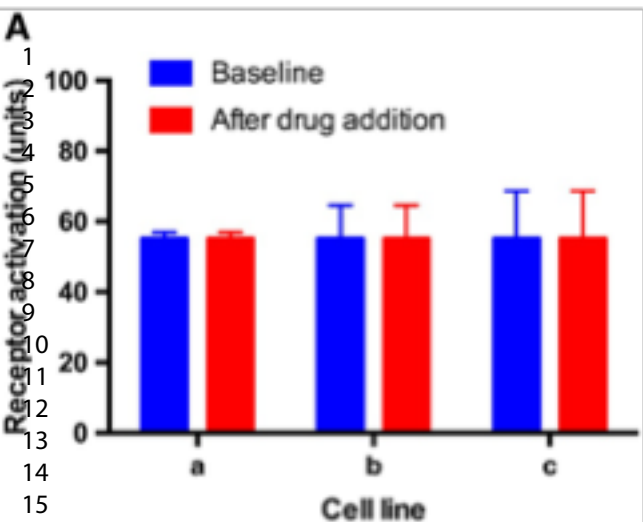
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Appendix 1

Cell/molecular biological Goldilocks zones

- The level of the signal molecule mTOR which ensures proper functioning of the anti-tumour agent *Treg* in immune cells: Zeng (2017) –
- Appropriate proximity to the ‘niche’ environment in the crypt region of the colon in order to ensure the persistence of stem cell potential: Walther and Graham (2014)
- The need for microbial communities to be neither too distant nor too close for high levels of emergent biosynthetic capacity to occur (Chiu et al 2014)
- The need to maintain a balance in the expression, activation and repression of Pattern Recognition Receptors in order to promote immune system homeostasis in the GI tract: (Ringel-Scala et al 2016)
- An appropriate balance of the highly gene-dosage-sensitive Notch pathway, a fundamental signalling mechanism required for differentiation and tissue homeostasis; too much or too little can lead to disease. (Braune and Lendahl 2016)
- ‘Goldilocks’, is the name applied to the Python computer package which takes a census of gene sequence data to identify genomic regions which are ‘just right’ (Nicholls et al, 2013)
- Mechanoresponsive proteins have Goldilocks zones of actin binding affinity in order to carry out cytoskeleton reorganisation in response to changing mechanical environments. (Schiffhauer et al 2015)
- Understanding *Mycobacterium tuberculosis* infection requires information on the balance of key chemokines/cytokines and their receptors and how loss of that balance can promote disease (Domingo-Gonzalez et al 2016).
- The ideal ‘Goldilocks’ Chemistry allows DNA and RNA to carry out their fundamental function in molecular heredity (Houlihan et al 2017)
- An allosteric Serine- Arginine protein -phosphatase platform which balances phosphorylation levels in a ‘goldilocks region’ is required for the proper sub-nuclear stage of a protein kinase protein splicing factor (Aubot et al 2017)
- Methyl-CpG-binding protein (MeCP2) must stay within a narrow range of expression – not too much, not too little – to be functionally ‘just right’ for proper epigenetic regulation in order to limit devastating phenotypic outcomes (immune defects underlying neurological deficits) (Boothby and Williams, 2012)
- Undifferentiated Embryonic Cell Transcription Factor (Utf1) ensures that conditions are precisely right for maintaining pluripotency and self-renewal in embryonic stem cells (Laskowski and Knoepfler 2012)

Tissue/whole body biology applied in medicine Goldilocks zones

- To minimise the risk of bone fractures, vitamin D levels need to be between 'lower' and 'higher', both of which increase the risk (Baughman and Lower 2014)
- A high and low proportion of carbohydrate in the diet is associated with increased human mortality, with minimal risk at 50-55% carbohydrate intake (Seidelmann et al 2018)
- Appropriate redox balance in striated muscle, where ROS production is counterbalanced by antioxidant capacity requires a Goldilocks zone, which scales down from the whole tissue to mitochondrial level: Alleman et al 2014)
- Optimal development of advanced therapeutic medicinal products for bone repair need to be neither too simple nor too complex (Leijten et al 2015)
- Appropriate timing, dose and regimen of estrogen exposure is required to promote beneficial effects on cognition (Koenle and Bimonte-Nelson, 2015)
- Vitamin C concentrations which are 'just right' (especially not unphysiologically high) are needed in order to interpret effects of the vitamin on human physiology (Padayatty and Levine, 2016)
- Recommendations for post-polypectomy surveillance should aim to target a Goldilocks zone (Ladabaum and Schoen, 2016)
- The need to balance fetal needs vs maternal supply during pregnancy in great apes and humans in terms of the level of inflammation; is essential during implantation; otherwise there is the risk of disorders such as gestational diabetes and choriodecidual inflammatory syndrome (Clancy, 2013).
- With regard to fluid management around the time of surgery – too little (pre- and post- operatively) is associated with inadequate organ perfusion and too much, with tissue oedema and surgical complications. Finding the 'Goldilocksian' 'just right' zone is the challenge (Cuthbertson, 2013).
- Judicious surgery for breast cancer indicates that a 2mm margin is superior to a narrower one in patients with Ductal Carcinoma In Situ and that bigger is not necessarily better (Jagsi 2016)
- Networks of neurones need to stay in a Goldilocks zone between 'too quiet' and 'too active' (Humphries 2016).
- The 'Goldilocks zone' of fatty acid metabolism is required to ensure that the relationship with cardiac function is just right. (Kerr et al 2017).

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- In emergency medicine a balance needs to be struck between the speed of treatment and its accuracy – sicker patients are more likely to benefit from intervention whereas less sick do not and may be harmed. It is necessary to get into the *Goldilocks zone*; the ‘just right’ balance between speed and accuracy (Fatovich, 2017)
- In the use of exercise to maintain joint homeostasis in the horse, too little or too much can result in joint derangement whereas just the right amount will provide optimal functioning of the joint (Milner 2017).
- In the treatment of perioperative blood pressure, the anaesthetist should aim at the ‘Goldilocks’ range, reminiscent of the optimal haemoglobin concentration, and avoid excursions in either direction (Sweitzer and Howell, 2017)
- ‘Goldilocks’ software is used in facilitating hearing-aid self-fitting *to allow user exploration and selection of preferred levels of overall output, low-frequency cut and high frequency boost*. (Boothroyd et al 2017).
- In the administration of oxygen in the clinical situation, the move is to avoid both excessive and inadequate therapy – moving away from the notion that more is always better and instead giving the least amount necessary (Martin and Grocott 2017).
- A ‘Goldilocks trial design’ constantly asks *‘Is the sample size too big, too small or just right?’* As an example, Broglio et al (2014) present a Bayesian adaptive design for a confirmatory trial to select a trial’s sample size based on accumulating data
- The Goldilocks dilemma in acute ischemic stroke asks which patients are ‘just right’ for endovascular treatments (Tansy and Liebeskind 2013)
- Excess or deficiency of retinoic acid leads to inner ear dysmorphogenesis via an effect on FGF3/1`1`2121FGF10 signalling; referred to as a Goldilocks phenomenon (Frenz et al 2010)
- For patients with newly diagnosed glioblastoma, the goal is to define the ‘Goldilocks zone’ for the optimal duration of adjuvant temozolomide (Grossman and Keleinberg 2017)
- Following lung injury, different progenitor cell populations can arise depending on the molecular environment – resulting in normal or aberrant alveolar repair. A key question is how to maintain a ‘Goldilocks zone’ of repair (Dean and Lloyd 2017) – nice diagram
- The design of inferior vena cava filters for the treatment of Venous thromboembolic disease relies on a ‘Goldilocks’ premise: i.e., make the device stable, (so it doesn’t migrate) but not too stable (so you can still retrieve it) (Magnowski et al 2017)

- Genetic variation in humans occurs through different types of alleles; at one extreme are mutations that cause Mendelian disease such as familial hypercholesterolemia arising from mutations in the LDL receptor with powerful phenotypic effects; at the other are common alleles (eg. ApoE) with small phenotypic effects. In the middle are 'Goldilocks alleles' (e.g., PCSK9) where the mutations are common enough to be useful in epidemiological analyses (in contrast to Mendelian) but still produce detectable biochemical effects. (Cohen, 2013)
- Fetal androgen production, especially testosterone, needs to be 'just right' to ensure the appropriate developmental trajectory of the fetus and offspring, while inappropriate fetal androgen or androgen signalling – both too little and too much - is associated with disorders of male reproductive development as well as being implicated in Polycystic Ovarian Syndrome in women (Fowler and O'Shaughnessy 2013).

Human Behaviour Goldilocks zones

- Social auditory stimuli intermediate between 'predictable' and 'complex' best serve the selective attention of 7-8-month old infants: Kidd et al (2016)
- An optimal amount of social interactivity of television watching promotes children's visual attention and word learning (Nussenbaum and Amso, 2016).
- When considering the wellbeing of adolescents, 'too little' digital screen use may deprive them of important social information and peer pursuits whereas 'too much' may displace other meaningful activities (Przybylski and Weinstein 2017)

Human educational training needs Goldilocks zones

- The degree of specialisation required to ensure the acquisition of professional competences in Paediatric Psychological training (Steele et al 2014)

Healthcare

- The 'Goldilocks point' in Palliative Care refers to exactly the right time to mobilise specialist hospital/palliative care services for the patient sub-group who will derive the most benefit. (LeBlanc et al 2014)
- The Goldilocks Principle is invoked in the regulation of healthcare to make sure it is not too little, nor too much but 'just right': Kemple (2016)

- The need for Children's Health Insurance to provide 'just the right health outcomes, just the right patient care experience and just the right costs': Szilagyi (2015)

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Going to extremes: the Goldilocks/Lagom principle and data distribution

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3 1 Going to extremes: the Goldilocks/Lagom principle and data distribution
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5 2 Henry J Leese ^{1*}, Thozhukat Sathyapalan ^{2,3}, Victoria Allgar ⁴, Daniel R Brison ^{5,6} & Roger G
6 3 Sturmeay ¹
7 4

8 5 1, Centre for Atherothrombosis and Metabolism, Hull York Medical School, University of Hull,
9 6 Hull, HU6 7RX, UK

10 7 2, Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University
11 8 of Hull, Hull, HU6 7RK UK

12 9 3, Department of Endocrinology, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK

13 10 4, Hull York Medical School, University of York, York YO10 5DD, UK

14 11 5, Maternal and Fetal Health Research Centre, Division of Developmental Biology and
15 12 Medicine, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of
16 13 Manchester, Manchester Academic Health Sciences Centre, St. Mary's Hospital,
17 14 Manchester, M13 9WL, United Kingdom

18 15 6, Department of Reproductive Medicine, St. Mary's Hospital, Manchester University NHS
19 16 Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, M13 9WL,
20 17 United Kingdom

21 18 * To whom correspondence should be addressed: henry.leese@hyms.ac.uk
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32 32 **Abstract**

33 23 Numerical data in biology and medicine are commonly presented as mean or median with
34 24 error or confidence limits, to the exclusion of individual values. Analysis of our own and
35 25 others' data indicates that this practice risks excluding 'Goldilocks' effects in which a
36 26 biological variable falls within a range between 'too much' and 'too little' with a region
37 27 between where its function is 'just right'; a concept captured by the Swedish term 'Lagom'.
38 28 This was confirmed by a narrative search of the literature using the PubMed Database,
39 29 which revealed numerous relationships of biological and clinical phenomena of the
40 30 Goldilocks/Lagom form including quantitative and qualitative examples from the health and
41 31 social sciences. Some possible mechanisms underlying these phenomena are considered.
42 32 We conclude that retrospective analysis of existing data will most likely reveal a vast number
43 33 of such distributions to the benefit of medical understanding and clinical care and that a
44 34 transparent approach of presenting each value within a data set individually should be
45 35 adopted to ensure a more complete evaluation of research studies in future.

46 36 **174 words**
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52 40 Going to extremes: the Goldilocks/Lagom principle and data distribution
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54 41 **Text**
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57 43 Introduction
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3 44 Numerical data in science and medicine have traditionally been presented as mean or
4 45 median values with standard errors or standard deviations. Such data commonly take the
5 46 form of tables, bar graphs or line graphs. However, as (1) point out, this practice poses a
6 47 problem since different distributions of data can lead to the same bar or line graph. This was
7 48 well illustrated recently by (2) who used illustrative data from a hypothetical experiment to
8 49 examine the impact of three different cell lines on drug receptor activation and showed that a
9 50 variety of distributions of individual data points can lead to similar bar graphs with the same
10 51 mean (Fig 1). This is because bar charts frequently do not convey major features of the
11 52 dataset adequately. As Figure 1 makes clear, away from using bar charts to visualize the
12 53 entire dataset is a necessary refinement that can increase the transparency and reporting of
13 54 data.

14 55 “ The extent of activation of a receptor in three cell lines a, b and c under baseline
15 56 (drug-naïve) conditions and following the addition of a drug is given in arbitrary units. The
16 57 same data sets are presented in three different ways: (A) bar chart, (B) grouped column
17 58 scatter plot with means and error and (C) before–after scatter plot. $n = 10$ (i.e. biological
18 59 replicates and not technical replicates). In this example, error bars represent the SEM
19 60 although authors should consider the sampling size and distribution of ‘ n ’ when choosing the
20 61 most appropriate way of showing experimental error [e.g. SD or confidence interval]”.

21 62
22 63 The attention paid to individual variation in cellular and molecular biological and clinical
23 64 studies is relatively recent, but has been well-known for many years to ecologists, especially
24 65 following the publication by Albert F. Bennett, in 1987, of an influential article entitled: *Inter-*
25 66 *individual variability: an underutilized resource*. Bennett, an ecological physiologist, pointed
26 67 out that mean values with confidence intervals about the mean, once published tend to ‘--
27 68 *take on a life of their own, and become the only point of analysis and comparison*’ to the
28 69 exclusion of the individual values, and their potential significance. Bennett referred to this
29 70 tendency as ‘*the tyranny of the Golden Mean*’, and as an alternative, advocated the analysis
30 71 of inter-individual variability, i.e., the full range of individual values, he considered could
31 72 provide the observer with a greater interpretative repertoire.

32 73 In the time since Bennett’s paper, there has been a movement away from the tyranny of the
33 74 mean in many areas of biology, notably in ecology (3). Examples are provided by Stephen J
34 75 Gould (4), who wrote an article on ‘*The median isn’t the message*’, Hayes and Jenkins (5) on
35 76 individual variation in mammals, and Lloyd-Smith (6) on the spread of epidemics of human
36 77 disease.

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3 79 Our interest in inter-individual variability arose particularly from research in which we have
4 80 been involved on (a) the development and metabolism of single preimplantation mammalian
5 81 embryos (DB, HL, RS) and (b) of glycaemic control in individual human subjects (TS).

8 82 (a) Development and metabolism of single preimplantation embryos

10 83 Data which illustrate the value of distributions rather than mean or median values were
11 84 provided by (7) who measured the consumption of the essential nutrient, pyruvate, by single
12 85 bovine preimplantation embryos at the zygote stage (1-cell fertilised egg; day 1 of
13 86 development). The experiments revealed considerable heterogeneity between individual
14 87 embryos such that it was possible to divide them prospectively into 3 groups - of 'high',
15 88 'intermediate' and 'low' pyruvate consumption at an early stage (day 2) - and track their
16 89 subsequent development to the blastocyst stage, a critical developmental endpoint. These
17 90 data indicated that intermediate values of pyruvate consumption correlated with viability
18 91 (capacity to form a blastocyst), though with considerable overlap between the categories.
19 92 Put another way, which takes account of this overlap, plotting individual values revealed the
20 93 existence of an optimal 'range' of metabolic activity. This concept was developed in a follow-
21 94 up paper (8) in which we proposed that the optimal range was equivalent to a 'Goldilocks
22 95 zone' or as it is known in Sweden, of 'lagom', meaning 'just the right amount', in which
23 96 embryos with maximum developmental potential are located.

24 97
25 98 (b) Glycaemic control

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27 100 Glycated haemoglobin (HbA_{1c}) is a marker of glycaemic control in patients with diabetes
28 101 which is commonly used in clinical practice. Indeed, (HbA_{1c}) is the recommended test for
29 102 diagnosing diabetes. (9). There is an association between the extent of high blood glucose
30 103 as measured by HbA_{1c} and the risk of death and of macrovascular and microvascular
31 104 disease in patients with type 2 diabetes (T2DM) (10). In the landmark United Kingdom
32 105 Prospective Diabetes Study, intensive glycaemic control that aimed to achieve a HbA_{1c} level
33 106 of 7% or below was associated with improved outcome in newly diagnosed patients with
34 107 type 2 diabetes (T2DM) (11). This finding was then extrapolated to all patients with T2DM,
35 108 and as a result, lower HbA_{1c} levels were recommended for management of patients with
36 109 T2DM. However, concerns arose as data from the Action to Control Cardiovascular Risk in
37 110 Diabetes (ACCORD) trial began to emerge showing increased all-cause mortality and
38 111 cardiovascular mortality in the intensive treatment group who were treated with
39 112 antihyperglycaemic agents aiming for a lower HbA_{1c} target of 6% compared with
40 113 conventional antihyperglycaemic treatment in patients with T2DM aiming for HbA_{1c} of 7-
41 114 7.9%. These results led to early termination of the trial (12). Further studies (13,14) have

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3 115 demonstrated that lower and higher mean HbA1c values were associated with an increased
4 116 risk of cardiovascular events and mortality suggesting a “Goldilocks’ or ‘lagom” state of
5 117 HbA1c is the optimal.
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9 119 Similar “U” shaped associations with HbA1c and all-cause mortality have also been shown
10 120 for type 1 diabetes (15). Even in patients without diabetes, extremes of glycaemia as
11 121 measured by HbA1c are associated with adverse clinical outcomes including cardiovascular
12 122 events and all-cause mortality. Similar increases in mortality in either extremes are seen
13 123 with body weight, blood pressure, birth weight, cholesterol and other cardiovascular risk
14 124 factors.
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20 126 Goldilocks and Lagom

21 127 The Goldilocks zone has been defined mathematically by (16) in the context of xenobiotic
22 128 ligand binding to nuclear receptors as a ‘*Non-monotonic receptor-mediated dose-response*
23 129 *curve*’ (NMDRC), and by (17) in the context of endocrine disrupting chemicals as ‘a
24 130 *response where the slope of the curve changes sign from positive to negative or vice versa*
25 131 *somewhere along the range of doses examined*’. These are valuable definitions because
26 132 they can be applied to all non-linear distributions including U-shaped, inverted U-shaped, J-
27 133 shaped, sigmoidal and reverse sigmoidal.
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34 134 The U-shaped curve is probably the most widely observed. It usually refers to the nonlinear
35 135 relationship between two variables, in particular, a dependent and an independent variable.
36 136 Because many analytical methods assume an underlying linear relationship, systematic
37 137 deviation from linearity can lead to bias in estimation of safe levels in exposure to nutrients,
38 138 drugs or toxic agents (for a discussion see section on *Mechanisms* below and (17)).
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43 140 How widespread is the presence of a Goldilocks zone in biology and medicine?

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45 141 We thought it might be instructive to discover how widely the notion of a ‘Goldilocks zone’ is
46 142 a feature of the wider biological literature, especially as applied to medicine. A
47 143 comprehensive search for information conducted on the *PubMed* database in early 2018
48 144 using the term ‘Goldilocks’ revealed 184 entries, all of which have been examined, together
49 145 with the grey literature. Only articles in English language were selected. A selection of 43 of
50 146 these publications has been presented (Appendix 1) as representative of the range of
51 147 phenomena which invoke the Goldilocks concept in order to increase biological and clinical
52 148 understanding. It should be emphasised that this is a narrative review rather than systematic
53 149 review and no judgement on the quality of these studies or of those which have been omitted
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3 150 is implied. Patient/public involvement: No members of the public, nor patients were involved
4 151 in the synthesis of this manuscript.

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8 153 Inspection of these examples reveals the wide range of biological and clinical phenomena in
9 154 which Goldilocks zones have been found including the health and social sciences which can
10 155 be qualitative rather than quantitative. It seems likely that a vast number remain to be
11 156 discovered and that authors could, in a relatively simple manner, derive added value from
12 157 their existing data by presenting distributions rather than median/mean values, and making
13 158 raw data available to the research community via online repositories. This would allow
14 159 systematic re-analysis by data scientists with an interest in the Goldilocks/Lagom concept.

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18 162 Mechanisms underlying the Goldilocks Principle and what is Lagom

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20 164 *Mechanisms which are global in scope*

21 165 We previously proposed an explanation that may account for Goldilocks/Lagom phenomena,
22 166 derived from our work on energy efficiency in early mammalian embryo development (8)
23 167 which made use of an account of general aspects of biological optimisation by (18). The
24 168 premise was that living things aim to function with the minimum input of energy, i.e., with
25 169 high energetic efficiency. To accomplish this will obviously require a threshold level of
26 170 metabolic activity to ensure a given process proceeds in an optimum, yet efficient manner,
27 171 while the upper limit will be set by the capacity to increase metabolism vs *'the energy*
28 172 *parsimony in almost everything (living things) do'* (18). The Goldilocks/Lagom zone will
29 173 obviously lie between these extremes. The boundaries will be set by homeostatic
30 174 mechanisms at all levels of organisation. Such boundaries will be flexible in order to allow for
31 175 the capacity to up- or down-regulate metabolism in response to stress. Responses of these
32 176 types have been usefully categorised by ecologists to distinguish (a) modest changes in
33 177 metabolism (up or down within the *optimum* (Goldilocks/Lagom) range) from which the
34 178 cell/organism can recover (the so-called *Pejus* range) and (b) extreme perturbation beyond
35 179 the optimum which shifts metabolism irreversibly into a *Pessimum* range which is fatal (see
36 180 Fig 1 in the work of Sokolova (19)

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38 182 Some *specific mechanisms* for the production of non-monotonic receptor-mediated dose-
39 183 response curves (NMDRCs) were well summarised by (17) in terms of the effect of
40 184 endocrine disrupting chemicals, notably Bisphenol A on cells in culture, whole organisms,
41 185 laboratory animals and human populations. Interestingly, it was reported that NMDRCs were

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3 186 common, comprising 20-30% of all studies examined, depending on the conditions; e.g., in
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5 187 vivo vs in vitro. Mechanisms considered included cytotoxicity (20), inhibition of cell
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7 188 proliferation (21); hormone receptors produced vs degraded (22); cell and tissue specific co-
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9 189 factors (23) and pharmacological effects. At the whole body level, examples of NMDRCs in
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11 190 nutrition are widespread, reflecting minimum requirements at the lower end of the distribution
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13 191 and toxicity at the higher, for example, vitamin A. Vandenberg (17) concludes that '*strong*
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15 192 *evidence for Non-monotonic receptor-mediated dose-response curves*' - - *question the*
16
17 193 *current risk assessment practice where 'safe' levels are predicted from high dose exposures*'

19 196 *Conclusion*

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22 198 There has long been a fixation in the biological and clinical research communities with
23
24 199 presenting data solely as measures of dispersion (means and medians) and of central
25
26 200 tendency (e.g., standard deviation and interquartile range). We believe that the retrospective
27
28 201 analysis of existing data could reveal numerous potential relationships with a
29
30 202 Goldilocks/Lagom pattern.

31 203 Interestingly, the editors of the British Journal of Pharmacology ' (2) '*will now require that,*
32
33 204 *where possible, numerical data (whether categorical or continuous), particularly involving*
34
35 205 *two sets or paired data, should be presented using scatter-plots, before-after graphs, and*
36
37 206 *other forms in which each individual 'n' value is individually plotted, rather than using bar*
38
39 207 *charts. Authors presenting data as bar charts should state that a scatter plot or before-after*
40
41 208 *charts did not reveal unusual or interesting aspects of the data not obvious from the bar*
42
43 209 *chart*'.

44 210
45 211 We believe the Journal should be complimented on this approach and urge all such journals
46
47 212 to adopt it.

48 213 *Author contributions:*

49 214
50 215 H J Leese; conceived the study, conducted literature searches and wrote the first draft. All
51
52 216 authors then commented on subsequent drafts. V Allgar; provided statistical advice, DR
53
54 217 Brison; contributed to the initial concept and provided new material, as did RG Sturmeay who
55
56 218 also prepared the manuscript for submission T Sathyapalan; contributed to initial concept;
57
58 219 provided new material and clinical expertise
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60 220

61 221 *Competing Interests:*

62 222 The authors have no competing interests to declare in relation to this work.
63
64 223

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3 315 Fig 1; An illustrative example of a comparison of cell lines is described in Figure 1, which
4 316 shows that bar charts do not give the reader adequate information on the variability and
5 317 distribution of each sampled 'n'.
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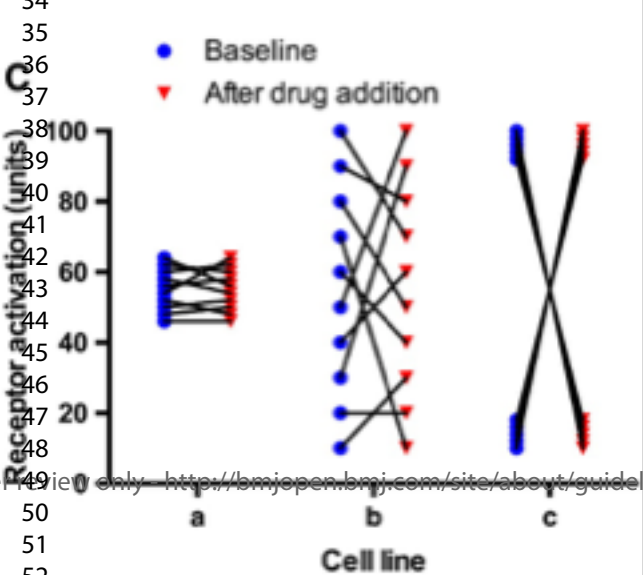
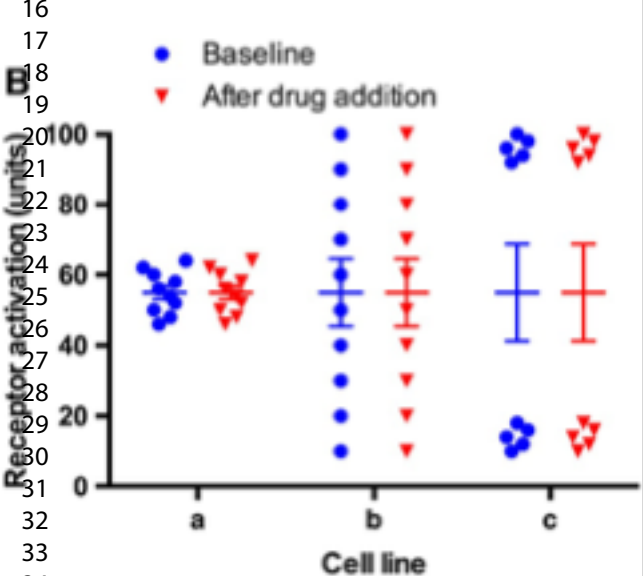
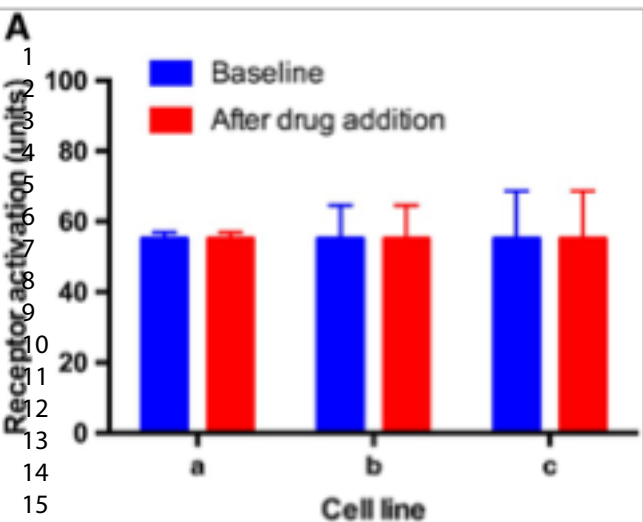
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For peer review only



Appendix 1

Cell/molecular biological Goldilocks zones

- The level of the signal molecule mTOR which ensures proper functioning of the anti-tumour agent *Treg* in immune cells: Zeng (2017) –
- Appropriate proximity to the ‘niche’ environment in the crypt region of the colon in order to ensure the persistence of stem cell potential: Walther and Graham (2014)
- The need for microbial communities to be neither too distant nor too close for high levels of emergent biosynthetic capacity to occur (Chiu et al 2014)
- The need to maintain a balance in the expression, activation and repression of Pattern Recognition Receptors in order to promote immune system homeostasis in the GI tract: (Ringel-Scala et al 2016)
- An appropriate balance of the highly gene-dosage-sensitive Notch pathway, a fundamental signalling mechanism required for differentiation and tissue homeostasis; too much or too little can lead to disease. (Braune and Lendahl 2016)
- ‘Goldilocks’, is the name applied to the Python computer package which takes a census of gene sequence data to identify genomic regions which are ‘just right’ (Nicholls et al, 2013)
- Mechanoresponsive proteins have Goldilocks zones of actin binding affinity in order to carry out cytoskeleton reorganisation in response to changing mechanical environments. (Schiffhauer et al 2015)
- Understanding *Mycobacterium tuberculosis* infection requires information on the balance of key chemokines/cytokines and their receptors and how loss of that balance can promote disease (Domingo-Gonzalez et al 2016).
- The ideal ‘Goldilocks’ Chemistry allows DNA and RNA to carry out their fundamental function in molecular heredity (Houlihan et al 2017)
- An allosteric Serine- Arginine protein -phosphatase platform which balances phosphorylation levels in a ‘goldilocks region’ is required for the proper sub-nuclear stage of a protein kinase protein splicing factor (Aubot et al 2017)
- Methyl-CpG-binding protein (MeCP2) must stay within a narrow range of expression – not too much, not too little – to be functionally ‘just right’ for proper epigenetic regulation in order to limit devastating phenotypic outcomes (immune defects underlying neurological deficits) (Boothby and Williams, 2012)
- Undifferentiated Embryonic Cell Transcription Factor (Utf1) ensures that conditions are precisely right for maintaining pluripotency and self-renewal in embryonic stem cells (Laskowski and Knoepfler 2012)

Tissue/whole body biology applied in medicine Goldilocks zones

- To minimise the risk of bone fractures, vitamin D levels need to be between 'lower' and 'higher', both of which increase the risk (Baughman and Lower 2014)
- A high and low proportion of carbohydrate in the diet is associated with increased human mortality, with minimal risk at 50-55% carbohydrate intake (Seidelmann et al 2018)
- Appropriate redox balance in striated muscle, where ROS production is counterbalanced by antioxidant capacity requires a Goldilocks zone, which scales down from the whole tissue to mitochondrial level: Alleman et al 2014)
- Optimal development of advanced therapeutic medicinal products for bone repair need to be neither too simple nor too complex (Leijten et al 2015)
- Appropriate timing, dose and regimen of estrogen exposure is required to promote beneficial effects on cognition (Koenle and Bimonte-Nelson, 2015)
- Vitamin C concentrations which are 'just right' (especially not unphysiologically high) are needed in order to interpret effects of the vitamin on human physiology (Padayatty and Levine, 2016)
- Recommendations for post-polypectomy surveillance should aim to target a Goldilocks zone (Ladabaum and Schoen, 2016)
- The need to balance fetal needs vs maternal supply during pregnancy in great apes and humans in terms of the level of inflammation; is essential during implantation; otherwise there is the risk of disorders such as gestational diabetes and choriodecidual inflammatory syndrome (Clancy, 2013).
- With regard to fluid management around the time of surgery – too little (pre- and post- operatively) is associated with inadequate organ perfusion and too much, with tissue oedema and surgical complications. Finding the 'Goldilocksian' 'just right' zone is the challenge (Cuthbertson, 2013).
- Judicious surgery for breast cancer indicates that a 2mm margin is superior to a narrower one in patients with Ductal Carcinoma In Situ and that bigger is not necessarily better (Jagsi 2016)
- Networks of neurones need to stay in a Goldilocks zone between 'too quiet' and 'too active' (Humphries 2016).
- The 'Goldilocks zone' of fatty acid metabolism is required to ensure that the relationship with cardiac function is just right. (Kerr et al 2017).

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3 • In emergency medicine a balance needs to be struck between the speed of
4 treatment and its accuracy – sicker patients are more likely to benefit from
5 intervention whereas less sick do not and may be harmed. It is necessary to get into
6 the *Goldilocks zone*; the ‘just right’ balance between speed and accuracy (Fatovich,
7 2017)
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- 9
10 • In the use of exercise to maintain joint homeostasis in the horse, too little or too
11 much can result in joint derangement whereas just the right amount will provide
12 optimal functioning of the joint (Milner 2017).
13
- 14 • In the treatment of perioperative blood pressure, the anaesthetist should aim at the
15 ‘Goldilocks’ range, reminiscent of the optimal haemoglobin concentration, and avoid
16 excursions in either direction (Sweitzer and Howell, 2017)
17
- 18 • ‘Goldilocks’ software is used in facilitating hearing-aid self-fitting *to allow user*
19 *exploration and selection of preferred levels of overall output, low-frequency cut and*
20 *high frequency boost.* (Boothroyd et al 2017).
21
- 22 • In the administration of oxygen in the clinical situation, the move is to avoid both
23 excessive and inadequate therapy – moving away from the notion that more is
24 always better and instead giving the least amount necessary (Martin and Grocott
25 2017).
26
- 27 • A ‘Goldilocks trial design’ constantly asks *‘Is the sample size too big, too small or just*
28 *right?’* As an example, Broglio et al (2014) present a Bayesian adaptive design for a
29 confirmatory trial to select a trial’s sample size based on accumulating data
30
- 31 • The Goldilocks dilemma in acute ischemic stroke asks which patients are ‘just right’
32 for endovascular treatments (Tansy and Liebeskind 2013)
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- 34 • Excess or deficiency of retinoic acid leads to inner ear dysmorphogenesis via an
35 effect on FGF3/1`1`2121FGF10 signalling; referred to as a Goldilocks phenomenon
36 (Frenz et al 2010)
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- 38 • For patients with newly diagnosed glioblastoma, the goal is to define the ‘Goldilocks
39 zone’ for the optimal duration of adjuvant temozolomide (Grossman and Keleinberg
40 2017)
41
- 42 • Following lung injury, different progenitor cell populations can arise depending on the
43 molecular environment – resulting in normal or aberrant alveolar repair. A key
44 question is how to maintain a ‘Goldilocks zone’ of repair (Dean and Lloyd 2017) –
45 nice diagram
46
- 47 • The design of inferior vena cava filters for the treatment of Venous thromboembolic
48 disease relies on a ‘Goldilocks’ premise: i.e., make the device stable, (so it doesn’t
49 migrate) but not too stable (so you can still retrieve it) (Magnowski et al 2017)
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- Genetic variation in humans occurs through different types of alleles; at one extreme are mutations that cause Mendelian disease such as familial hypercholesterolemia arising from mutations in the LDL receptor with powerful phenotypic effects; at the other are common alleles (eg. ApoE) with small phenotypic effects. In the middle are 'Goldilocks alleles' (e.g., PCSK9) where the mutations are common enough to be useful in epidemiological analyses (in contrast to Mendelian) but still produce detectable biochemical effects. (Cohen, 2013)
- Fetal androgen production, especially testosterone, needs to be 'just right' to ensure the appropriate developmental trajectory of the fetus and offspring, while inappropriate fetal androgen or androgen signalling – both too little and too much - is associated with disorders of male reproductive development as well as being implicated in Polycystic Ovarian Syndrome in women (Fowler and O'Shaughnessy 2013).

Human Behaviour Goldilocks zones

- Social auditory stimuli intermediate between 'predictable' and 'complex' best serve the selective attention of 7-8-month old infants: Kidd et al (2016)
- An optimal amount of social interactivity of television watching promotes children's visual attention and word learning (Nussenbaum and Amso, 2016).
- When considering the wellbeing of adolescents, 'too little' digital screen use may deprive them of important social information and peer pursuits whereas 'too much' may displace other meaningful activities (Przybylski and Weinstein 2017)

Human educational training needs Goldilocks zones

- The degree of specialisation required to ensure the acquisition of professional competences in Paediatric Psychological training (Steele et al 2014)

Healthcare

- The 'Goldilocks point' in Palliative Care refers to exactly the right time to mobilise specialist hospital/palliative care services for the patient sub-group who will derive the most benefit. (LeBlanc et al 2014)
- The Goldilocks Principle is invoked in the regulation of healthcare to make sure it is not too little, nor too much but 'just right': Kemple (2016)

- The need for Children's Health Insurance to provide 'just the right health outcomes, just the right patient care experience and just the right costs': Szilagyi (2015)

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