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Ra T, B, J. 2021 C, a, a *in vitro* a. *Interface Focus* **11**: 20200069.

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Time is inherent to biological processes. It determines the order of events and the speed a
is essential for the size, function and shape of developing organisms.

Biological clocks need to keep track of multiple timescales, and cells need to be in synchrony to build tissues and organs during development and homeostasis. How tempo is encoded in the genome and how organisms coordinate the development of different organs remain unknown. Growing evidence suggests that tempo can be set by autonomous mechanisms in individual cells during development [1,2], but little is known in adult tissues. Likewise, local and global tempo must be coordinated for appropriate developmental outcomes and during homeostasis in the adult. Intra-organ and inter-organ communication mechanisms have started to be deciphered in the regulation of developmental growth and the homeostatic maintenance of tissues [3–5].

Gene regulatory networks (GRNs) play a central role in development. Gene expression programmes are controlled by transcriptional regulators that, together with the cis-regulatory elements to which they bind, integrate external cues and coordinate the spatial and temporal elaboration of developmental programmes [6]. Experimentally, GRNs have been described based on gain and loss-of-function studies of transcription factors and the identification of cis-regulatory elements that drive tissue-specific gene expression profiles. However, most of the methodologies to study transcription factor function have a poor temporal resolution, making it difficult to understand GRNs quantitatively and dynamically. This is starting to change. Recent efforts are beginning to measure mRNA and protein levels and their turnover to

number. During the subsequent compensatory growth, somite differentiation was delayed as somites started to form at E8. From E10.5 onwards, somitogenesis accelerated resulting in the correct somite number by E11.5 [25–27]. Moreover, the for-

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Limbs represent one of the best-studied systems in evolution and development. Although they show a well-defined sequence of temporal events, such as the proximo-distal patterning of the limb bud and the chondrification of skeletal elements, they have undergone extensive evolutionary diversification in different species [43]. Some of this diversification appears to depend on changes in timing [44]. Limbs develop from the flanks of the trunk into three proximo-distal main segments in a proximo-distal timely manner.

the base of bud-like structures and mature cell types migrate to the central structure of the cyst [61]. The speed at which cells in these organoids differentiate appears to be species-specific. For example, the generation of specialized goblet cells in intestinal organoids from stem cells in mouse cells takes approximately 2 days, whereas human goblet cells emerge around day 5 [79]. It would be interesting to systematically measure the tempo in the differentiation trajectories in comparable organoid models of mouse and human.

Similar to developmental organoids, these *in vitro* systems offer an unprecedented opportunity to investigate cell-autonomous and coordinated mechanisms responsible for the speed of progression. Whether the differences in developmental tempo between species reflects differences in the homeostatic processes that maintain mature organs in adult animals remains to be determined. The ability to understand the pace of progression during homeostasis may in turn

biological processes but is likely to provide the means to engineer and refine methods to generate specific cell types for research and therapeutic applications.

Data a . Data for figure 3 are available from AnAge (https://genomics.senescence.info/species/) and electronic supplementary material from [83].

. T.R. conceived the manuscript. T.R. and J.B. wrote the manuscript.

C . We declare we have no competing interests.

. The authors are supported by the Francis Crick Institute, which receives its core funding from Cancer Research UK, the UK Medical Research Council and the Wellcome Trust (all under FC001051). T.R. received funding from an EMBO long-term fellowship (grant no. ALTF 328-2015). T.R. and J.B. are also funded by the Wellcome Trust (grant no. 215116/Z/18/Z).

A . We thank M. Joaquina Delás, Miki Ebisuya and Néstor Saiz for providing feedback.

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1. E a M, B, J. 2018 W a a ? *Development* (*Cambridge, England*) **14**, 164368. (:10.1242/ 164368)
2. B L, S B. 2020 T a a a . *Preprints* **2020**, 2020060168. (:10.20944/ 202006.0168. 1)
3. C CC *et al.* 2015 O, a a , a a . *Cell* **1 1**, 277–290. (:10.1016/ .2015.02.016)
4. R -D A, Ma L, Ba S, Z H, J AL. 2018 C - a a a , a a - a . *PLoS Biol.* **1**, 2005086. (:10.1371/ a. .2005086)
5. B S *et al.* 2018 P53 a TOR a , a a . *Nat. Commun.*, 1763. (:10.1038/ 41467-018-04167-)
6. D MJ, B, J. 2020 R a , a a : a . I *Current topics in developmental biology*, . 239–