Regarding the Lesson posted by Booth et al, there are a few important points to make in order to avoid confusing students.

First, the lac operon is not homeostatic (at least as the term is commonly understood), it is inducible. The operon is repressed by the constituative expression *lacI*, which encodes the lac repressor protein. It is induced under particular conditions, specifically the absence of a more efficient energy source and the presence of lactose (mammalian milk sugar). This confusion could be addressed by introducing some historical background on process, known as diauxie – a recent review by Blaiseau & Holmes (2021) might be useful.

Second, induction of the lac operon relies upon stochastic (noisy) processes that arise from the small number of repressor molecules per cell. This has been nicely modeled in the paper by Vilar et al (2003) that would be useful to consider. I have used their model in presenting the lac operon in biofundamentals (chapter 9, pp. 192-195). It speaks to the ability of organisms to probe and respond to changes in their environment.

Difficulties in understanding such "random" (i.e. stochastic) processes widespread and have been documented and discussed in Garvin-Doxas et al (2008). In this context, I have found that the studies of Elowitz et al (2002) are particularly useful in introducing students into the concept of stochasticity (as well as the molecular mechanisms involved). In fact they use the lac promoter in their studies.

More specifically, I question whether referring to stochastic events as due to "leakiness" helps students understand the molecular level processes involved? A leaky faucet is different mechanistically from one that turns on and off sporadically and stochastically, which is what the lac operon appears to do - see Vilar et al (2003)

An appreciation of the ubiquity of stochastic processes at the cellular level is central for developing an understanding of differential gene expression revealed most dramatically by single cell RNA SEQ and related studies (Kærn et al., 2005; Nishimura et al., 2015). A recent paper by Braun (2021) makes this point in the context of determinism and free will (see also Rolls and Deco, 2010).

Sincerely,
Mike Klymkowsky

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