On the numbers and division rates of stem cells in human tissues

Augusto Gonzalez
Instituto de Cibernetica, Matematica y Fisica, Calle E 309, La Habana, Cuba

Both the fraction of stem over differentiated cell numbers, \(N_s/N_d\), and the cell division rate, \(m_s\), experience relatively large variations (three decades) when different human tissues are considered. However, in a two-dimensional plot points are not randomly scattered. Two groups of tissues and a “transition region” at \(m_s \approx 8/\text{yr}\) are apparently identified. I present an analysis of the data from the point of view of the master equations for the number of cells and the rate of energy consumption under tissue homeostasis.

**Introduction.** In a recent work [1, 2], with the purpose of correlating stem-cell numbers and division rates with the lifetime risks of cancer in human tissues, a set of values for these stem-cell magnitudes was compiled. Apart from any criticism [3], the data reveal some general trends that are worth analysing.

First, the data show relatively large variations. For example, the stem-cell division rate in colon cripts is estimated by the authors as 73/year, whereas for bronchioalveolar cells the rate is around 0.07/year, i.e. three orders of magnitude smaller. Similar variations are exhibited by the quotient \(N_s/N_d\) between the stem and differentiated cell numbers in the tissues. Table I contains a summary of the data.

Two comments should be added with regard to the data in Tab. I. First, \(N_d\) is approximated by the total number of cells (the data provided in Refs [1] and [2]). And second, we use a small, but nonzero, division rate for neurons and glial cells [4].

In spite of the large variations, in a two-dimensional plot points are not randomly scattered, as shown in Fig. 1. Two groups or clusters of tissues are apparent.

On the other hand, in each group of tissues, the magnitude \(N_s/N_d\) seems to be a smooth function of \(m_s\). I draw dashed lines in Fig. 1 in order to guide the eyes. If we follow these dashed lines, the global dependence is univoque, that is for a given value of \(N_s/N_d\) there is a unique \(m_s\). The exception is the region \(m_s \approx 8/\text{yr}\), where there is an abrupt jump.

| Type I tissues          | \(N_s/N_d\) | \(m_s\) (1/yr) |
|------------------------|-------------|----------------|
| Epidermis              | 0.032       | 7.6            |
| Breast                 | 0.013       | 4.3            |
| Prostate               | 0.007       | 3              |
| Pancreatic cells       | 0.025       | 1              |
| Hepatocytes            | 0.0125      | 0.9            |
| Epithelium Gallbladder | 0.01        | 0.584          |
| Thyroid cells          | 0.0075      | 0.09           |
| Bronchioalveolar cells | 0.0028      | 0.07           |
| Bone cells             | 0.0016      | 0.066          |
| Neural cells           | 0.0016      | < 0.01         |

| Type II tissues         | \(N_s/N_d\) | \(m_s\) (1/yr) |
|------------------------|-------------|----------------|
| Epithelium Colon       | 0.007       | 73             |
| Small int.             | 0.006       | 36             |
| Epithelium Duodenum    | 0.006       | 24             |
| Epithelium Esophagus   | 0.002       | 33             |
| Epithelium Head and Neck | 0.001   | 21             |
| Germ cells Testis      | 0.0003      | 5.8            |
| Blood cells            | 0.000045    | 12             |

**TABLE I.** Data, coming from Refs. [1] and [2], for the ratio of stem over differentiated cell numbers, \(N_s/N_d\), and the stem cell division rate, \(m_s\), for different human tissues.

**FIG. 1.** (Color online) Two-dimensional plot of the data contained in Table I. Type I tissues are represented by blue circles, whereas red squares denote type II tissues. Dashed lines and a vertical line with \(m_s = 8/\text{yr}\) are drawn as references. The bottom panel is a linear axis representation, where data clustering is more apparent.

**Master equations for the number of cells.** In order to analyze the data, I write master equations for the number of cells. I use a very simple model, in which there
are only three cell categories: stem, transit or progenitor, and differentiated. Their numbers are \( N_s \), \( N_t \) and \( N_d \), respectively. The equations read:

\[
\begin{align*}
\frac{dN_s}{dt} &= (m_s - d_s)N_s, \\
\frac{dN_t}{dt} &= d_sN_s + (m_t - d_t)N_t, \\
\frac{dN_d}{dt} &= d_tN_t - r_dN_d.
\end{align*}
\]

\( m_s \), as mentioned, is the mitotic division rate of stem cells. \( d_s \), on the other hand, is the rate at which the stem lineage differentiates to transit cells. The same convention applies to the magnitudes \( m_t \) and \( d_t \). Finally, \( r_d \) is the replacement rate of differentiated cells in the tissue.

Under stationary conditions (homeostasis) the r.h.s. of these equations are zero, leading to:

\[
\begin{align*}
m_s &= d_s, \\
d_sN_s &= (d_t - m_t)N_t, \\
d_tN_t &= r_dN_d.
\end{align*}
\]

Combining these equations, we arrive to a condition, expressing the constance of the number of cells, that is the number of new cells equals the number of replaced ones:

\[
m_sN_s + m_tN_t = r_dN_d. \tag{3}
\]

The stationary values for \( N_s \) and \( N_t \) are determined from:

\[
\begin{align*}
\frac{N_t}{N_d} &= \frac{r_d}{d_t}, \\
\frac{N_s}{N_d} &= \frac{d_t - m_t}{m_s} \frac{N_t}{N_d} = (1 - m_t/d_t) \frac{r_d}{m_s}. \tag{4}
\end{align*}
\]

I assume that \( r_d \) is characteristic of a tissue. It depends on physiological and functional aspects. The other parameters, \( m_s \), \( m_t \) and \( d_t \) are partially determined by \( r_d \) or shall fulfill additional requirements. For example, when we move from the lung tissue to the epidermis, \( r_d \) notably increases. Thus, according to Eq. (4), the mitotic rates or the cell number ratios, or both, shall increase also.

**Interpreting the data.** I shall assume also that the following relations hold for the number of cells and the mitotic rates:

\[
N_s < N_t < N_d, \quad m_s < m_t. \tag{5}
\]

The small number of stem cells probably is, along with other characteristics like asymmetric DNA replication, tissue architecture, etc [5], an evolutionary strategy to minimize DNA damage related to somatic mutations. \( N_s \) and \( m_s \) should, thus, be kept as small as possible. In cases where anyone of these magnitudes takes relatively high values, then the second one is decreased, as clearly shown in the lower panel of Fig. [1].

Minimization of DNA damage probably requires that \( N_t \) should be kept small also.

We shall see below, on the other hand, that small numbers of stem and transit cells reduce energy expenditure in the tissue under homeostatic conditions.

Because of Eqs. (3): \( N_s/N_d = r_d/d_t \approx r_d/m_t \), meaning that \( m_t \) should be much greater than \( r_d \) in order to minimize \( N_t \). However, there is an upper bound for \( m_t \) related to the minimal time of around 10 h for DNA replication in eukaryotes [6]. That is,\n
\[
m_t \leq 730/\text{yr}. \tag{6}
\]

High values of \( m_t \) have a negative impact on DNA damage, which is probably compensated by the finite lifetime of transit cells.

The lower branch in Fig. [1] the red squares, seem to be tissues for which \( m_t \) is near its limiting value, given by Eq. (6).

Indeed, let us consider the extreme points in the lower branch. In the colon, \( N_s/N_d \approx 0.007 \) and the turnover rate is \( r_d \approx 60/\text{yr} \) [7]. A rough estimation of \( N_t \) from \( N_t/N_d \geq 10 N_s/N_d \approx 0.07 \), leads to \( m_t \approx r_d/0.07 \approx 850/\text{yr} \), above the upper bound. Thus, \( m_t \) should be fixed to the upper limit, and \( N_t/N_d \) estimated from \( r_d/m_t \).

The second extreme point corresponds to blood, for which \( N_s/N_d \approx 0.000045 \), and \( r_d \approx 5.3 \). Notice that there is a wide variation in the turnover rates of blood cells, ranging from a few days for white cells to a few months for red cells [7]. The given \( r_d \) is a number-weighted average. The rough estimation \( N_t/N_d \geq 10N_s/N_d \approx 0.00045 \) leads to \( m_t \leq 11700/\text{yr} \), a meaningless result. The actual \( m_t \) should be close to the limiting value.

In conclusion, type II tissues are characterized by \( m_s \geq r_d \) and \( m_t \) near its upper limit, 730/yr.

On the other hand, the upper branch of Fig. [1] the blue circles, correspond to tissues for which \( m_t \) is not close to its limit, given by Eq. (6). For example, in the epidermis, with \( N_s/N_d \approx 0.032 \), \( N_t/N_d \approx 0.32 \) [1], and \( r_d \approx 18/\text{yr} \) [7], the division rate is \( m_t \approx 54/\text{yr} \). Notice also that \( m_s \approx 7.6/\text{yr} < < r_d \) in the present case.

**Rates of energy expenditure under homeostatic conditions.** The energy per unit time spend by a cell under stationary conditions is to be written as a linear function of the mitotic rate: \( g = g_1 + g_2 m \). The \( g_1 \) and \( g_2 \) constants are tissue specific. In the differentiated cells, not exhibiting proliferative capacity, \( m_d = 0 \), and only the first term is present. For the whole tissue, we get:
The first term, \( g_1 N_d \), comes from the differentiated cells. The second, \( g_2 r_d N_d \), from cell replacement. The last two terms are minimized when \( N_s \) and \( N_t \) take relatively small values.

Fig. 2 upper panel, shows how the data would be represented in the \( N_t/N_d \) vs \( m_t \) plane. The representation is schematic because actual values are very scarce. Due to the conditions \( m_t \gg m_s \) and \( N_t \gg N_s \), I may write a simplified Eq. \( \text{(3)} \): \( N_t/N_d \approx r_d/m_t \). Dotted lines in the figure, corresponding to fixed values of \( r_d \), come from this relation.

In the lower panel, on the other hand, I draw the magnitude \( g_1 N_t/N_d \), neglecting the contribution of stem cells for the above mentioned reasons. Data for the energy consumption rates are taken from Ref. [8] that is 224.5 Kcal/Kg/day for the liver, 36.8 for the gastro-intestinal tract, and 14 for other tissues. The dotted lines in the present case, drawn for reference purposes only, seem to suggest three levels of power expenditure by the transit cells. This result requires further study and more precise data.

**Concluding remarks.** Minimization of the number of stem and transit cells is probably a biological requirement. For the transit cells, this implies the condition \( m_t \approx d_t \gg r_d \) to hold, as seen in Eqs. \( \text{(4)} \). On the other hand, with regard to the stem cells, in the data presented in Refs [1] and [2] two sets are clearly identified. For \( m_s > 8/yr \), the tissues are characterized by \( m_s \gg r_d \) and \( m_t \) near its upper bound, determined by the minimal DNA replication time, whereas for \( m_s < 8/yr \), the tissues have \( m_s \gg r_d \) and a rate \( m_t \) well below the upper bound. These "branches" have counterparts in Eqs. \( \text{(4)} \) as different ways of minimizing the number of cells.

Preliminary results seem to suggest three levels of power expenditure by the transit cells in the tissues under study.

**Acknowledgments.** Support from the National Program of Basic Sciences in Cuba, and from the Office of External Activities of the International Center for Theoretical Physics (ICTP) is acknowledged.

---

1. Cristian Tomasetti and Bert Vogelstein, Variation in cancer risk among tissues can be explained by the number of stem cell divisions, Science 347, 78-81 (2015).
2. Cristian Tomasetti, Lu Li, Bert Vogelstein, Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention, Science 355, 1330-1334 (2017).
3. Michael O’Callaghan, Cancer risk: Accuracy of literature, Science 347, 729 (2015).
4. Kirsty L. Spalding, Ratan D. Bhardwaj, Bruce A. Buchholz, Henrik Druid, and Jonas Frisen, Retrospective Birth Dating of Cells in Humans, Cell 122, 133-143 (2005).
5. Steven A. Frank, Dynamics of Cancer: Incidence, Inheritance, and Evolution (Princeton University Press, Princeton, 2007).
6. B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter, Molecular Biology of the Cell (Garland Science, New York, 2002).
7. Ron Milo and Rob Phillips, Cell Biology by the Numbers (Garland Science, New York, 2015).
8. China M. Kummitha, Satish C. Kalhan, Gerald M. Saidel and Nicola Lai, Relating tissue/organ energy expenditure to metabolic fluxes in mouse and human: experimental data integrated with mathematical modeling, Physiological Reports 2, e12159 (2014).