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On strain and stress in living cells

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ABSTRACT

Recent theoretical simulations of amelogenesis and network formation and new, simple analyses of the basic multicellular unit (BMU) allow estimation of the order of magnitude of the strain energy density in populations of living cells in their natural environment. A similar simple calculation translates recent measurements of the force–displacement relation for contacting cells (cell–cell adhesion energy) into equivalent volume energy densities, which are formed by averaging the changes in contact energy caused by a cell's migration over the cell's volume. The rates of change of these mechanical energy densities (energy density rates) are then compared to the order of magnitude of the metabolic activity of a cell, expressed as a rate of production of metabolic energy per unit volume. The mechanical energy density rates are 4–5 orders of magnitude smaller than the metabolic energy density rate in amelogenesis or bone remodeling in the BMU, which involve modest cell migration velocities, and 2–3 orders of magnitude smaller for innervation of the gut or angiogenesis, where migration rates are among the highest for all cell types. For representative cell–cell adhesion gradients, the mechanical energy density rate is 6 orders of magnitude smaller than the metabolic energy density rate. The results call into question the validity of using simple constitutive laws to represent living cells. They also imply that cells need not migrate as inanimate objects of gradients in an energy field, but are better regarded as self-powered automata that may elect to be guided by such gradients or move otherwise.
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1. Introduction

When a cell moves, there are two possibilities: it can move as an inanimate object driven by external forces (energy gradients) or it can move as an animate entity using energy generated within itself as part of its own metabolic function. The term “automaton” will refer here to a cell whose motion is not that of an inanimate object but rather is enacted by energy that is internally derived and practically unlimited within the context. The cell may also proliferate, differentiate, or die as an automaton, i.e., perform these actions using internal power, although possibly timed by an external stimulus.

In regard to motion, cells may act inanimately or as automata at different time scales. When a force is applied rapidly to living skin, the skin and the subcutaneous tissues deform quickly as a viscous, nonlinear, inanimate material. The response of the tissue can be summarized in a constitutive law relating stress to strain, and engineering stress analysis can predict, for example, the deflection of the skin for a given force and its bounce back after the force is removed. In contrast, when skin is cut, cells act as living entities, migrating towards the cut and proliferating to effect healing. Cell motion is relatively slow: crucially, the cell motions occur over time frames that are long compared with the time required for significant metabolism

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within the cell. Thus there is adequate time for the cell itself to generate the forces that must be applied to surrounding extra-cellular matrix (ECM) or other cells for it to move, by converting chemical potential energy into mechanical work.

This article addresses the question of when it is reasonable to regard a cell as an inanimate subject of external forces and when it is not by comparing the mechanical energy required for cell migration in certain natural contexts with the energy available to the cell from its metabolism. The energy of metabolism is expressed as a rate of energy production per unit volume or "metabolic energy density rate." This may be directly compared with the "strain energy density rate," which is the rate of change of the mechanical energy per unit volume that occurs as cells change their state of strain (i.e., deform). These terms will be abbreviated to "metabolic energy rate" and "strain energy rate" henceforth, with the fact that they refer to volume energy densities implicit.

Having determined the relative energy rates for some representative cases of organogenesis, using results from recent theories of cell migration in amelogenesis and network formation, together with new estimates for osteoblasts in the basic multicellular unit (BMU) and previously published estimates for tumor growth, we discuss the implications for how cell behavior should be represented.

2. The energy of life vs. mechanical energy

2.1. Metabolic energy rates

The total energy involved in the metabolic activity of a cell can be measured through the time rate of production of adenosine-5′-triphosphate (ATP) from glucose, which is accompanied by a free energy change of approximately 7.3 kcal mol^{-1}, with some minor variation with pH and other factors (Crofts, 2013). In osteoblasts, for example, the total rate of ATP production has been estimated at 1700 nmol h^{-1} per 10^6 cells (comprising 900 nmol h^{-1} per 10^6 cells by glycolysis and 800 nmol h^{-1} per 10^6 cells by oxidative phosphorylation) (Komarova et al., 2000). Thus the energy produced per cell is approximately 5.2×10^{-8} J h^{-1}. The volume of an osteoblast is approximately 2000–4000 μm^3. Thus the rate of metabolic energy produced per unit volume ("metabolic energy rate") is approximately in the range

$$\dot{G}_{\text{met}} = 4-7\times10^{-15}\ \text{Jmm}^{-3}\ \text{s}^{-1} \tag{1}$$

where G_{met} is a volume energy density and the dot indicates time differentiation. The metabolic energy rate for different cells will show some variability, tending to be higher in cells such as osteoblasts that are actively secreting matrix and in cells in proximity of dense vascular supply. The value of Eq. (1) is a reasonable estimate of the capacity for metabolic activity of cells involved in organogenesis. Besides osteoblasts, cells of particular interest below are ameloblasts, which are responsible for the formation of dental enamel. Since secretory-stage ameloblasts produce large quantities of amelogenin and have a similar volume to osteoblasts (although very different shape), the value of Eq. (1) is probably also a reasonable estimate of their metabolic energy rate. A previously published estimate of metabolic energy rate for cancer cells in a growing tumor yielded values up to $\dot{G}_{\text{met}} = 7\times10^{-15}$ Jmm^{-3} s^{-1}, coinciding with the upper end of the range in Eq. (1) (Fig. 3f of Narayanan et al. (2010)).

When cells are interspersed with extra-cellular matrix (ECM), the metabolic energy per unit of volume will be diminished by the fraction of all volume occupied by the ECM. In the cases to be considered, this volume fraction is small and its effect will not change order-of-magnitude estimates.

2.2. Strain energy rates

Recent analyses of cell movements in certain cases of organogenesis have yielded quantitative estimates of the strain and strain rates experienced by cells. Some calculations yield global strain states, which is to say spatially averaged strain variations over populations of 10^2–10^7 cells and any ECM with which they may be interspersed, while others yield local strains around individual cells. When combined with estimates of the mechanical stiffness of cells and any ECM with which they may be interspersed, the strain predictions yield estimates of the strain energy rate, which is the rate at which cells do the mechanical work required to deform as they migrate. The strain energy rate is evaluated either averaged over a population or averaged over a single cell, depending on whether the strains are global or local.

Stiffness estimates are based on a simple assumed linear relationship between strain and mechanical stress (linear elasticity or Hooke's law). The strain energy estimates are therefore upper bounds, because linear elasticity is likely to be correct only when the strain is changing rapidly in time; for the rates of change of strain typical of living cells, the stiffness and therefore the strain energy rate are likely to be lower (Appendix A).

Assume that a region of a cell population is subject to a state of strain. The strain state will generally be some combination of tension in one or more directions, compression in one or more directions, and one or more components of shear. Adopting Voigt notation (Timoshenko and Goodier, 1970; Mura, 1982), the mechanical strain energy per unit volume for the cells G_{el} can be written

$$G_{\text{el}} = \frac{1}{2}(\sigma_{11}\varepsilon_{11}+\sigma_{22}\varepsilon_{22}+\sigma_{33}\varepsilon_{33}+\sigma_{23}\varepsilon_{23}+\sigma_{31}\varepsilon_{31}+\sigma_{12}\varepsilon_{12}) \tag{2a}$$

where ε_{ij} and σ_{ij} are strain and stress components, respectively (Appendix A). The time derivative of this, i.e., the strain energy rate, can be written in a form convenient to the current purpose of estimating orders of magnitude as

$$\dot{G}_{\text{el}} = \eta E\varepsilon_0\dot{\varepsilon}_0+\eta' E\gamma_0\dot{\gamma}_0 \tag{2b}$$

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