Corrigendum

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Corrigendum to: Statistical mechanics of cell decision-making: the cell migration force distribution

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The corrections correspond to the Section 3 of the original article. I will present the whole section but corrections will be indicated in red.

A free-energy principle: the least microenvironmental uncertainty prior

The above arguments can be translated in a statistical mechanics formulation, as for instance in the work of Karl Friston [1]. My central idea is that the cell decides on its phenotype by virtue of minimally sampling its microenvironment. As stated above, my goal is to optimize the cell's prior and at the same time minimize the uncertainty of a cell's microenvironment. This can be mathematically translated into finding the appropriate intrinsic state pdf $p(\mathbf{x})$ that maximizes the joint entropy of cell intrinsic and extrinsic variables

$$\max_{p(\mathbf{x})} S(\mathbf{X}, \mathbf{Y}), \tag{1}$$

where $S(\mathbf{X}, \mathbf{Y}) := -\int d\mathbf{x}d\mathbf{y}\, p(\mathbf{x}, \mathbf{y}) \ln p(\mathbf{x}, \mathbf{y}) = S(\mathbf{X}) + S(\mathbf{Y}|\mathbf{X})$.

The corresponding variational principle that follows reads:

$$\frac{\delta}{\delta p(\mathbf{X})}\left[S(\mathbf{X}, \mathbf{Y}) - \lambda\left(\int d\mathbf{x} p(\mathbf{x}) - 1\right)\right] = 0, \tag{2}$$

where the $\frac{\delta}{\delta p(\mathbf{X})}$ denotes the functional derivative operator and λ a Lagrange multiplier for the normalization constraint. The solution of Eq. (2) is the equilibrium pdf:

$$p(\mathbf{x}) = \frac{e^{-\beta S(\mathbf{Y}|\mathbf{X}=\mathbf{x})}}{Z}, \tag{3}$$

where $Z = \int d\mathbf{x} e^{-\beta S(\mathbf{Y}|\mathbf{X}=\mathbf{x})}$ the corresponding normalization factor. The last equation is very interesting since it shows the equilibrium distribution of the cell's intrinsic states is the one that confers the least uncertainty of

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microenvironmental conditions (see below for further elaboration). Interestingly, this type of distributions are called entropic priors in the context statistical inference [4] and have also been applied in statistical physics and thermodynamics [5]. Please note that I arbitrary introduced the parameter β as an "inverse temperature", that quantifies the compliance of a cell to LEUP. Also, any additional biological knowledge will be translated into Lagrange constraints of the free-energy minimisation.

To illustrate the above result, let us assume that the distribution $p(\mathbf{y}|\mathbf{x})$ follows the normal distribution $\mathcal{N}(\mu_y(\mathbf{x}), \sigma_y^2(\mathbf{x}))$. Then the mutual entropy reads

$$S(\mathbf{Y}|\mathbf{X}=\mathbf{x}) = \ln(2\pi\sigma_y^2(\mathbf{x}))^{1/2},$$

and the Eq. (3) respectively becomes:

$$p(\mathbf{x}) = \frac{\sigma_y^{-\beta}(\mathbf{x})}{\int d\mathbf{x}\,\sigma_y^{-\beta}(\mathbf{x})}. \tag{4}$$

This last equation is exactly the normalized square root of Fisher's Information for the second moment, i.e. $\sqrt{\mathcal{I}(\sigma_y(\mathbf{x}))} \propto 1/\sigma_y(\mathbf{x})$ [2]. Given the latter our equilibrium distribution (4) coincides with a normalized Jeffrey's prior distribution, for $\beta = 1$. Jeffrey's prior represents the definition of non-informative Bayesian prior in classical statistics [3].

Substituting the equilibrium pdf (3) into the cell intrinsic state entropy, we obtain:

$$S(\mathbf{X}) = -\int d\mathbf{x}\,p(\mathbf{x})\,\ln\frac{e^{-\beta S(\mathbf{Y}|\mathbf{X}=\mathbf{x})}}{Z} = \beta S(\mathbf{Y}|\mathbf{X}) + \ln Z. \tag{5}$$

The above is a fundamental thermodynamic identity of LEUP where the first term denotes the system's total phenotypic internal energy $U = \langle S(\mathbf{Y}|\mathbf{X}=\mathbf{x})\rangle_{p(\mathbf{x})}$ which is the average microenvironmental uncertainty sensed by a cell. The last term represent a phenotypic free energy $F = -\beta^{-1}\ln Z$. Since microenviromental entropy $S(\mathbf{Y}|\mathbf{X})$ acts as a energy/potential function, for $\beta > 0$ it should be *decreasing in time*, typically to a specific steady state value, in order to ensure relaxation to the steady state distribution Eq. (3). Please note that the entropy $S(\mathbf{Y}|\mathbf{X})$ is a coarse-grained microenvironment representation over a cell's sensing area.

References

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