Brouwer 關於時間是意識的原始直覺的主張已從復雜系統物理學的角度考慮。
基於實數過程定義的時間連續體涉及這種直覺主義的骨架範疇，它應該與測量問題有關。
測量過程的多分辨率層次對應於時間算子，它是布魯塞爾熱力學學院開發的複雜系統的形式主義。
概括層次結構統計特性的小波域隱馬爾可夫模型已被證明在各種應用中非常有用，包括語音識別和人工智能。
由於表示的變化是時間的操作功能，該模型提供了外部和內部心理物理學之間的切換。
內在心理物理學是感覺和神經活動之間的關係，對應於結構信息的識別，這種結構信息已反映在時域統計複雜性的增加上。
最佳測量對應於最顯著的增加，這是系統自組織的指標，它代表了時間和意識之間的明顯聯繫。

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The Lack of Systems Biology In-between the HLA-C and COVID-19 Severity

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The association between the COVID-19 severity and the *HLA-C*04:01* allele is the most replicated finding across Human Leukocyte Antigen (HLA) variants and diverse populations including the Armenian. The results have led to several hypotheses on the *HLA-C*04:01* allele contribution to the causative mechanisms. Thus, to unravel the systems biology underlying this genetic association, the present study aimed at identifying the *HLA-C*04:01*-related aberrations in whole blood leukocyte transcriptome, which may blueprint the severe pathophysiology of COVID-19.

Thus, we have performed DESeq2 bioinformatics and Gene Set Enrichment Analysis of RNA-sequencing data of a large publicly available cohort of 100 patients [Gene Expression Omnibus: accession ID GSE157103]. HLA-genotypes were acquired from the imputed data by Warren and Birol [PeerJ 2021]. Using univariate models of blood leukocyte transcriptomes of COVID-19 patients, we assessed differentially expressed genes (DEGs) between several clinical and demographical groups. The highest number of DEGs (over 3000) was found when groups of patients admitted and not admitted to the Intensive Care Units (ICU) have been compared. The biological processes, such as the positive regulation of both NK-mediated cytotoxicity and interferon-gamma production, as well as T cell activation. Relatively high numbers of DEGs were found associated with age and some ethnic groups. Nevertheless, only 15 DEGs were found between males and females. A comparison of HLA-C*04:01 carriers and non-carriers revealed only 3 DEGs, i.e. *ANKS1B*, *PLA2G7*, and *DOCK6* (P_{FDR} <0.05), with the inability to underpin any biological system. Moreover, in a multivariate model with five parameters (i.e. ICU status, *HLA-*

*C*04:01* carriage, age, sex, ethnicity) blood leukocyte transcriptomes did not exhibit pronounced differences between carriers and non-carriers of the *HLA-C*04:01* allele. Besides, we found that the expression profile of HLA genes is associated with COVID-19 severity, age, and ethnicity but not with HLA-C*04:01 carriage and sex. For the last attempt to identify transcriptome changes associated with *HLA-C*04:01* carriage, we used the GTEx portal to find QTLs linked to *HLA-C*04:01*. Remarkably, >12 eQTLs and sQTLs were enriched for processes such as TAP-independent antigen processing and presentation of endogenous peptide antigen via HLA class I, protection from NK-mediated cytotoxicity, innate immune response to other organisms. However, none of the GTEx *HLA-C*04:01*-linked blood leukocyte eQTLs (i.e. *HCG27*, *NOTCH4*, *TCF19*, *TRIM39*, *MIR6891* and *XXbac-BPG181B23.7*) was differentially expressed between *HLA-C*04:01* carrier and non-carrier patients, indicating that transcriptome aberrations due to the COVID-19 could disrupt QTLs associations reported for human control samples. In line with the lack of evidence related to Systems Biology, we found that due to high HLA-C expression, *HLA-C*04:01* may disrupt HLA-C mediated immune protection harnessing NK cells and causing NK *hyporesponsiveness* through KIR2DL1 inhibitory receptors.

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HLA-C 和 COVID-19 嚴重性之間缺乏系統生物學

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COVID-19 嚴重程度與 HLA-C*04:01 等位基因之間的關聯是人類白細胞抗原 (HLA) 變體和包括亞美尼亞人在內的不同人群中重複最多的發現。 結果導致了關於 HLA-C*04:01 等位基因對致病機制的貢獻的幾個假設。

因此，為了揭示這種遺傳關聯背後的系統生物學，本研究旨在識別全血白細胞轉錄組中與 HLA-C*04:01 相關的畸變，這可能會描繪出 COVID-19 的嚴重病理生理學。

因此，我們對 100 名患者的大型公開可用隊列 [Gene Expression Omnibus：登錄號 GSE157103] 的 RNA 測序數據進行了 DESeq2 生物信息學和基因集富集分析。 HLA 基因型是從 Warren 和 Birol [PeerJ 2021] 的估算數據中獲得的。 我們使用 COVID-19 患者血液白細胞轉錄組的單變量模型，評估了幾個臨床和人口統計學群體之間的差異表達基因 (DEG)。 當比較入住和未入住重症監護病房 (ICU) 的患者組時，發現 DEG 數量最多（超過 3000）。 生物過程，例如 NK 介導的細胞毒性和乾擾素-γ 產生的正調節，以及 T 細胞活化。 發現相對較多的 DEG 與年齡和某些種族相關。 儘管如此，在男性和女性之間只發現了 15 個 DEG。 HLA-C*04:01 攜帶者和非攜帶者的比較顯示只有 3 個 DEG，即 ANKS1B、PLA2G7 和 DOCK6 (PFDR <0.05)，無法支撐任何生物系統。 此外，在具有五個參數（即 ICU 狀態、HLA-C*04:01 攜帶、年齡、性別、種族）的多變量模型中，血液白細胞轉錄組在 HLA-C*04 攜帶者和非攜帶者之間沒有表現出明顯差異 :01 等位基因。 此外，我們發現 HLA 基因的表達譜與 COVID-19 的嚴重程度、年齡和種族有關，但與 HLA-C*04:01 的攜帶和性別無關。 最後一次嘗試識別與 HLA-C*04:01 運輸相關的轉錄組變化，我們使用 GTEx 門戶網站查找鏈接到 HLA-C*04:01 的 QTL。 值得注意的是，超過 12 個 eQTL 和

sQTL 被豐富用於 TAP 獨立抗原加工和通過 I 類 HLA 呈遞內源肽抗原、防止 NK 介導的細胞毒性、對其他生物體的先天免疫反應等過程。 然而，GTEx HLA-C*04:01 連鎖的血液白細胞 eQTL（即 HCG27、NOTCH4、TCF19、TRIM39、MIR6891 和 XXbac-BPG181B23.7）均未在 HLA-C*04:01 攜帶者和非攜帶者之間差異表達 - 攜帶者患者，表明 COVID-19 導致的轉錄組畸變可能會破壞人類對照樣本報告的 QTL 關聯。
由於缺乏與系統生物學相關的證據，我們發現由於 HLA-C 高表達，HLA-C*04:01 可能會破壞 HLA-C 介導的利用 NK 細胞的免疫保護，並通過 KIR2DL1 抑制受體導致 NK 反應遲鈍。

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