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Exploring Markov Processes Variational Approach for Dynamics Prediction of Antiviral Peptides

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Peptides are known to exhibit significant antiviral properties. This work focuses on the DENV-2 peptide (CGYGLC) in aqueous solution, notable for its anti-Dengue potential. Understanding its conformational dynamics is vital for assessing its structural and functional behavior. Molecular dynamics (MD) is commonly used for such studies, but is computationally intensive and time-consuming. To address this, we investigate the simulation of a reduced fraction of the total simulation time.

We employ the Variational Approach for Markov Processes (VAMP) to analyze the peptide's conformational dynamics. The initial structure of DENV-2 was obtained using AlphaFold2 [2] and simulated for a total of 10 ns (equivalent to 50000 frames) with AMBER [1]. Dihedral angles define the polypeptide chain's spatial conformation and are key to a peptide's secondary and tertiary structure. These angles are derived by transforming Cartesian coordinates from molecular dynamics simulations. Torsion angles (ψ and ϕ) are favored because of their lower dimensionality, which is more closely related to the intrinsic dynamics of the system. Each dihedral angle is the torsion between four consecutive atomic positions. Their temporal evolution is modeled as a multivariate time series:

$$\Phi(t+1) = F(\Phi(t)) + \eta(t) \tag{1}$$

where $\Phi = (\phi\ \psi)^T$, with $\phi = (\phi_1, \ldots, \phi_{m-1})$ and $\psi = (\psi_1, \ldots, \psi_{m-1})$, such that $\forall \psi_i, \phi_i \in [-\pi, \pi]$. Thus, $\Phi \in [-\pi, \pi]^{2(m-1)}$, where m is the peptide's amino acid sequence length. $\eta(t)$ is a noise term at time t, and F is an unknown non-linear function.

As the state variables are atomic coordinates, we determine the evolution of the expected value of an observable function Φ applied to these variables, $\mathbf{E}[\Phi(x_{t+\tau})]$, to be:

$$\mathbf{E}\left[\Phi(x_{t+\tau})\right] = K^{\mathsf{T}}\mathbf{E}\left[\Phi(x_t)\right] \tag{2}$$

Here, τ is the lag time, ensuring Markovian dynamics by capturing the slowest time scales. Matrix K, the best Koopman operator approximation in the observable-generated subspace, is found via the VAMP fundamental theorem [4] as $K = C_{00}^{-1}C_{01}$. The canonical correlation matrices are $C_{00} = \mathbb{E}_t[\Phi(x_t)\Phi(x_t)^T]$ (autocorrelation at t), $C_{01} = \mathbb{E}_t[\Phi(x_t)\Phi(x_{t+\tau})^T]$ (time-lagged correlation linking initial and future states), and $C_{11} = \mathbb{E}_{t+\tau}[\Phi(x_{t+\tau})\Phi(x_{t+\tau})^T]$ (autocorrelation at $t+\tau$).

To predict dihedral angles at each time step (shifted by lag time $\tau = 0.002$ ps, or 1 frame), a Koopman operator is used. Let $\{\Phi_t\}_{t=0}^{n-1}$ be the molecular dynamics data and $\{\hat{\Phi}_t\}_{t=1}^{n}$ the

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Koopman predictions. The prediction follows [3]:

$$\hat{\Phi}_{t+\tau} = (V^{\mathsf{T}})^{-1}\Sigma U^{\mathsf{T}}(\Phi_t - \mu_0) + \mu_t \tag{3}$$

where $\hat{\Phi}_{t+\tau}$ is the predicted observable at $t+\tau$; Φ_t is the system state at t; μ_0 and μ_t are mean state variable values at initial time and time t, respectively. U, Σ, V are matrices from the Singular Value Decomposition (SVD: right singular vectors, singular values, left singular vectors, respectively), and $(V^{\mathsf{T}})^{-1}$ is the inverse transpose of V.

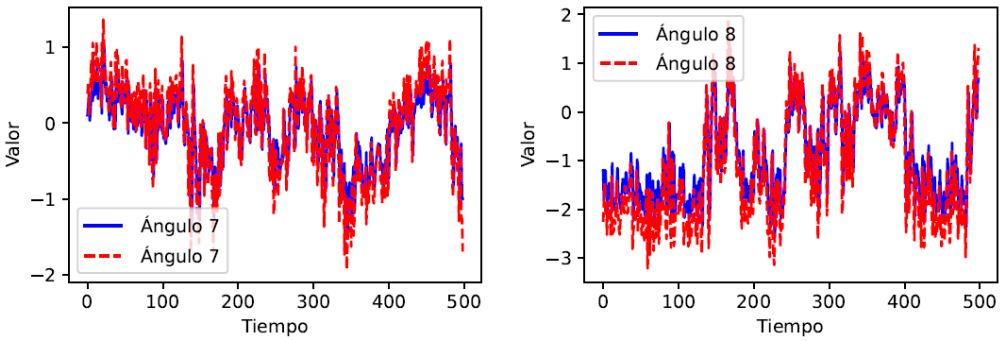

Figure 1: First Case of Prediction. The lag time is $\tau = 0.002$ ps. Source: Authors.

Figure 1 superimposes the molecular dynamics simulation and the Koopman operator prediction (blue). The dihedral angle dynamics (red) are accurately captured for this peptide when using the same τ for simulation and prediction.Further analyses are required to adapt the technique for accurate predictions over larger time intervals.

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